IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CIVIL NO. 13-CV-4507(CCC)

IN RE: DEPOMED PATENT LITIGATION

TRANSCRIPT OF
PROCEEDINGS
(Public)

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Newark, New Jersey
March 21, 2016

B E F O R E:

THE HONORABLE CLAIRE C. CECCHI,
United States District Judge

Pursuant to Section 753 Title 28 United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above-entitled proceedings.

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W I T N E S S E S

THE COURT: Let's talk about your agenda for today. What do we have going on? I know that we've had the weekend. In case there's any changes in plan.

MR. CONNOLLY: Your Honor, the first witness today will be Dr. Buvanendran. He is going to testify about non infringement and invalidity of the '130. We expect him to go about an hour and 15 on direct and obviously the cross. At that point Dr. Buvanendran will be the last witness on behalf of the defendants.

THE COURT: Okay.

MR. SITZMAN: The cross is probably be an hour plus. I would think that we would probably end up at lunchtime by the time we're done with Dr. Buvanendran.

THE COURT: That sounds fine.

MR. SITZMAN: After lunch we will have Dr. Bernstein who is the polymorph expert who will be with us.

THE COURT: All right. Sounds good. Anyone else for today or that's it? That should fill out the day, I'm assuming.

MR. SITZMAN: Yes.

THE COURT: What are we planning for tomorrow? Any thoughts yet? And if you don't have them, that's fine. We will check in with you at the end of the day.

MR. SITZMAN: No, I think we've disclosed it. Dr. Roush is coming. He is a medicinal chemist, synthetic

chemist, organic chemist. He will be testifying. I feel like he is going to last the majority if not all of the day.

THE COURT: All right. So he will be with us for awhile. Sounds good. All right. Let's start with the first witness. Actually you know what before we do that, let's get the appearances.

(Whereupon the attorneys entered their appearances)

MR. CONNOLLY: Before we get started, I believe that defendants counsel have an objection to one portion of one slide and a full slide of the other. The discussion of the objection and the response thereto, I think we will raise issues that are confidential. It relates to testimony that was given earlier in the case which was sealed so --

THE COURT: Understood.

A S O K U M A R B U V A N E N D R A N, sworn and testifies as follows:

DIRECT EXAMINATION BY MR. CONNOLLY:

MR. CONNOLLY: The defendants would ask that the courtroom be sealed for this discussion and ultimately, your Honor, the beginning of Dr. Buvanendran's testimony. After a very short introduction he is going to go directly into the non infringement. So we would ask that the courtroom be sealed for the same reasons that we sealed it before.

THE COURT: That's fine. Let's seal the

courtroom so we can address the issue.

THE COURT: All right. Let's just make sure who's in the room. Let's have the plaintiffs rise. Is that your group? Grunenthal and Depomed. Yes.

MR. SITZMAN: Yes.

THE COURT: Let's do the defendants. Actavis. All right. Roxane and Alkem. All right. Thank you. The courtroom is sealed. The transcript is sealed too.

(Whereupon the hearing was sealed).

MR. CONNOLLY: Your Honor, I think we are done with the infringement portion. I will turn to the invalidity portion. So, if your Honor would like to unseal the court, now is the time to do that.

THE COURT: Let's do that. This portion of the transcript will be unsealed from this point forward. We will physically unseal the courtroom now.

(Whereupon the following was heard in open court)*

THE COURT: Thank you. We may begin.

MR. CONNOLLY: Thank you, your Honor.

Q. Let's turn to the next slide if we could, slide 22. Now, doctor, have you considered the validity of the '130 patent claims 1, 2, 3 and 6?

A. Yes, I have.

Q. Okay and what does demonstrative 22 referencing in DTX 75 refer to?

A. So in the left-hand column it has all the defendants Alkem, Actavis and Roxane talking about claims 1 and 2 where the claims 1 and 2 talks about polyneuropathic pain and claims two is the salt of the Tapentadol. And Alkem has claims 3 and 6. And claims 3 and 6 specifically talk about patients with polyneuropathic pain and diabetic polyneuropathic pain. And claim 6 talks again about diabetic polyneuropathic pain.

Q. Did you consider the legal standards that were applicable in connection with your -- withdrawn.

You were going to talk about two different versions of invalidity today correct, right?

A. Yes.

Q. And the first is the first version, obviousness type double patenting?

A. Yes, sir.

Q. Did you consider the legal standard applicable to an obviousness type double patenting standard?

A. Yes, I did.

Q. Okay. Let's turn to slide 23. And could you please inform the Court as to what is it you intend to describe to the Court about the legal standard obviousness type double patenting?

A. As I said, I'm not a lawyer here, but, I want to talk about the two issues, the latter issued patent and the earlier issued patent is commonly owned.

And the second issue I am going to be talking about is claims of the latter patent are obvious over the claim of the earlier issued patent in this matter. I'm talking about '130 patent, claims 1, 2, 3 and 6 which is in 2007. While the '593 patent claim 117 is in 1994.

Q. Okay. And let's turn to slide 24. Did you also consider legal standards that were applicable in connection with the question of whether the later claims of the '130 patent were obvious in light of the earlier claim 117 of the '593 patent?

A. Yes.

Q. And what were the standards that you applied?

A. So, the subject matter of the claims as a whole would have been obvious for a person of ordinary skill in the art at the time of invention and they would consider some relevant factors.

Q. Were you asked to take in account other considerations for obviousness?

A. Yes. The scope and content of the prior art. The differences between the prior art and the claim at issue. And the level of ordinary skill in the art and secondary considerations.

Q. Okay. Any other legal considerations that you took into account in forming your opinion?

A. Yeah, a person of ordinary skill of art must be

motivated and have a reasonable expectation of success in achieving the claimed subject matter.

Q. Let's turn to slide 25.

In your consideration of the obviousness type double patenting issue, did you look at whether the patents were commonly owned?

A. Yes, I did. If I may have the next slide.

Q. What did you conclude in that regard? We are looking at slide 26 which references DTX 1346 and DTX 75.

A. So on the left-hand column of that slide it has the '593 patent. It is again assigned to Grunenthal. On the right side it has a patent '130 which is assigned to Grunenthal again. So it's assigned to the same company.

Q. Okay. So let's turn to slide 27. So, are you indicating there that one of the two elements of the obviousness type double patenting test has been met?

A. Yes.

Q. Please turn to the next slide, slide 28. Slide 28 is a reference to the '593 patent and it references DTX 1346, right?

A. Yes. In this slide I just wanted to show that the '593 patent was issued and the priority date for that was July 23, 1994 and the patent was '593.

Q. And what is your understanding of the stated priority date of the '130 patent claims?

A. The '130 patent is 2007.

Q. Okay. Let's turn to slide 29 if we could. Slide 29 references DTX 1346.

What do you have up on slide 29?

A. This is a Claim eight of that '593 patent where a method of treating aq mammal suffering from pain, said method comprising administering to said mammal an effective analgesic of a 1-phenyl-3-dimethyl-aminopropane compound.

And if you go down the patent it's contained in the 117 claim which this compound is Tapentadol.

Q. Let's turn to slide 30.

What have you prepared in slide 30?

A. Well, I decided to put the two patents side by side. On the left-hand column you have '593 and on the right-hand side you have patent '130 with claim one.

Q. Okay. And you've prepared some highlighting on there.

Are there any differences between the scope of claim 117 of the '593 patent and claim one of the '130 patent?

A. Yeah, I just wanted to put the differences in yellow. You can see the words are mammal on the '593 and in '130 it's called the subject. And there's practically no differences. And I also understand there's no dispute among the parties between the two words.

Q. Okay. And you noted some differences that were highlighted in light blue.

Could you please tell the Court about those?

A. Yes, the difference in '593 is highlighted as pain. And in '130 it talks about polyneuropathic pain.

Q. Okay. And we will come back to that in a second. There's also you've highlighted on the left analgesic amount and pain inhibiting amount.

Are those differences that are material in your opinion?

A. They are not. They are the same.

Q. Okay. All right. Now, I want to come back to the word "pain" that's contained in the '593 patent and turn to slide, to the next slide, slide 31.

What did the word "pain" mean in claim 117 of the '593 patent as of 1994?

A. The umbrella of pain back in 1994 included the concepts of nociceptive pain and neuropathic pain which is essentially the mechanisms or the pathophysiology, where the pain is originating from.

In 1994 it was believed that it was considered neuropathic and nociceptive and it is considered so even to date.

Q. And I think you answered this. In your answer, you referenced the mechanism of pain. What did you mean by that?

A. The mechanism and pathophysiology tells the practicing, the healthcare provider on the origin of the type of pain and

how the pain is being transmitted and being perceived. And so you can formulate appropriate treatments for these patients.

Q. And, Dr. Buvanendran, what is your understanding of whether the meaning of the word "pain" in 1994 is different from the meaning of the word "pain" in 2007 as persons of skill in the art understood those terms?

A. There's no difference in definition wise.

Q. You've testified so far about nociceptive pain and the mechanism of pain and neuropathic pain.

With regard to the two types of pain you've identified on demonstrative 31, would a person of ordinary skill in the art understand any additional classifications of pain?

A. Yes. As I've said before, you could -- the neuropathic pain, patients with neuropathic pain could be mononeuropathy or polyneuropathy. And again that will mean one nerve or multiple nerves in the polyneuropathy.

On the other hand, nociceptive pain which has an example of surgical pain or you hit your hand and you have specific pain around the effected part, could also be somatic or visceral. Somatic meaning an extremity or visceral meaning inside the abdomen or interabdominal contents.

Q. Let's turn if we could turn to demonstrative 32.

Now, what did you intend to illustrate on slide 32?

A. So, a person of ordinary skill in the art when they utilize the term "pain" it meant both nociceptive and

neuropathic pain back in 1994 and it is true even now. In addition, the '593 patent, the summary of the invention talks about here which are suitable for the treatment of severe pain without giving rise to the side effects which are typical of opioids.

Q. All right. Let's turn to slide 33, sir.

Now, you've put up there the '130 patent, DTX 75 claims 1 and 2. Are they different?

A. The claim one talks about the method of treating polyneuropathic pain in a subject suffering from therefrom. And the said method comprising administering to said subject an effective polyneuropathic pain inhibiting amount. And it talks about the hydrochloride salt in claim two.

Q. And let's turn to slide 34 that you prepared. I'm going to ask you what you were intending to illustrate in slide 34?

A. I was just trying to make an illustration here talking about the umbrella term of pain and the '593 claim, '593, claim 117, 1994 talks about this umbrella of pain. And in that umbrella there's a small subpopulation of patients. The '130 patent claims 1 and 2 which talks about polyneuropathic pain.

Q. And does the description of the various pain conditions that you've described in demonstrative slide 34, inform your or illustrate your opinion with respect to obviousness?

A. Yes.

Q. And as of March 2007, would a person of ordinary skill in the art have found the subject matter of claims 1 and 2 of the '130 patent obvious in light of claim 117 of the '593?

A. Yes. I just want to say this is all talking about severe pain.

Q. Okay. Let's turn to demonstrative 35. What additional limitation does claim three of the '130 patent contain as compared to claim one?

A. So, the claims 3 and 6, they both talk about diabetic polyneuropathic pain where claims one and two talks about polyneuropathic pain.

Q. Let's turn to slide 36 if we could. I'm going to ask you to describe for the Court what you were attempting to illustrate in slide 36?

A. So, similar to what I said before, there is a big umbrella of term for pain or severe pain, the '593 claim 117. And in this there is a small subpopulation which is the claim '130, claims 3 and 6, which is diabetic peripheral neuropathy patients.

Q. Is there any distinction in your mind between claims 3 and 6 of the '130 patent that reference diabetic polyneuropathic pain?

A. No.

Q. As a person -- withdrawn. As of March of 2000 how would a person of ordinary skill in the art compare the scope

of claims 117 of the '593 versus claims 3 and 6 of the '130 patent?

A. A person would assume it to be obvious.

Q. Okay. And what proportion of patients that you see in your clinical practice who suffer from polyneuropathic pain are suffering from diabetic polyneuropathic pain?

A. So, among the patients who have polyneuropathic pain, probably diabetes is probably one of the common reasons for polyneuropathy.

Q. Let's turn to slide 37. Slide 37 has the second column saying a later-issued claim would have been obvious in view of the earlier-issued claim, with a check box there.

What is your ultimate opinion with respect to obviousness type double patenting with respect to the '130 patent?

A. Obvious for a person of ordinary skill in art back in in 2007 to look at the '593 claim and see it's obvious.

Q. Let's, I'm going to ask you to turn to slide 38. And Dr. Buvanendran, what is your understanding of how the plaintiffs in this case contend a person of ordinary skill in the art would understand the term pain as of 1994 as it appears in claim 117 of the '593 patent?

A. So, it is my understanding that the plaintiffs allege that in the '593 when they meant the word "pain", they meant nociceptive pain.

Q. And only nociceptive pain?
A. That was what the plaintiffs allege.
Q. Do you recall what evidence of plaintiffs relied upon in support of that position?
A. I believe it was Dr. Ossipof who wrote in his report that when they talk about pain in 1994, he meant nociceptive pain.
Q. And do you recall what evidence Dr. Ossipof cited in support of his opinion.
A. Yes, I did look up the reference. I believe it's the Hammond reference where he talks about pain as only nociceptive pain.
Q. Mr. Haw, can you put up DTX 1576, please?
And Dr. Buvanendran, can you identify what this is?
A. So, this is a book chapter that was in Issues in Pain Measurement that I believe was published in I believe 1989.
Q. And Mr. Haw, could you put up plaintiffs, turn to Page 70 of DTX 1576 and call out the section entitled Nomenclature.
Dr. Buvanendran, is this the portion of Dr. Hammond's book chapter that Dr. Ossipof relied upon in his expert report?
A. Actually he just relied on the first statement which reads "the terms, pain and nociception, are frequently used interchangeably".
Q. Do you agree that Dr. Hammond's chapter of DTX 1576

supports or concludes that as of 1994 the ordinary meaning of pain referred only to nociceptive pain?

A. No, I do not agree.

Q. Does Dr. Hammond provide a definition of pain in 1576?

A. Yes. If you go further down in the same paragraph of the nomenclature, he talks about pain refers to both affective and a sensory sequellae of a noxious stimulus.

Q. Does that definition of pain include or exclude neuropathic pain?

A. That includes neuropathic pain as well.

Q. And why is that?

A. Because if you go down further, he talks about, she talks about the word hyperalgesia.

Q. Where is that?

A. It is highlighted there, the "hyperalgesia denotes increased sensitivity and reactivity to a noxious stimulus".

Q. And what does the next sentence say?

A. "It may also denote increased sensitivity to non-noxious stimulus".

Q. What is hyperalgesia?

A. So, hyperalgesia is when there is noxious stimulus, the response is normal. And when the response is higher than expected, then it is called hyperalgesia. So, a simple example would be a neuropathic pain patient would have hyperalgesia as a hallmark.

Q. Okay. And for what type of pain does hyperalgesia appear?

A. Neuropathic pain.

Q. And why therefore does the definition of pain in the Hammond reference DTX 1576 at Page 70 include neuropathic pain?

A. Because back in 1989 it was well-known that hyperalgesia existed and neuropathic pain and nociceptive pain existed.

Q. Okay. Now, thank you, Dr. Buvanendran.

Let's go back to slide 38 if we could please, Ted. Let's put aside for a moment your testimony that the chapter at DTX 1576 supports your position that the ordinary usage of pain in 1994 included both nociceptive and neuropathic pain.

If pain, the word "pain" as it appears in claim 117 of the '593 patent were restricted to nociceptive pain, would that affect your opinions regarding the obviousness of claims 1, 2, 3 and 6th of the '130 patent?

A. No, because there is in the literature that says that opiate and opioid like medications can be utilized for the treatment of neuropathic pain.

Q. You referenced literature. Were you referencing literature with respect to a particular time frame?

A. Yes, the time frame I picked up is 2007.

Q. Okay. And so is it your testimony that there was substantial literature prior to 2007 which talked about the

efficacy of opioid and opioid like compounds?

A. Yes.

Q. For polyneuropathic and neuropathic pain?

A. Yes. In addition to my clinical practice, I use opioid and opioid like medications for the treatment of neuropathic and polyneuropathic pain patients.

Q. Why did you consider literature about opioid and opioid like drugs as of March 2007?

A. That was the time the patent was filed.

Q. Okay. And what was relevant to the specifics of opioid and opioid like drugs with respect to the patent, the '130 patent?

A. The '130 patent was talking about Tapentadol which is an opioid and opioid like mechanism of action. And therefore I considered all the opioids in this concern analysis.

Q. Let's if we could turn to slide 39, Ted.

Okay. Now is slide 39 one of the references that you, pre-2007 references that you considered and testified about?

A. Yes. This is a reference from June of 1998 published in Neurology, the Harati article, DTX 1605.

Q. What did the Harati article say, if anything, that informed your opinion in this case?

A. So, this is a study of diabetic peripheral neuropathy painful patients. And this is a randomized controlled trial where they gave either Tramadol for the treatment of pain or

they gave a placebo for the patients, about 131 patients randomized into the two groups. And they followed these patients for a 42-day period.

Q. And what conclusions, if any, did they reach?

A. The conclusion of the study of the randomized controlled trial was that the results of the placebo controlled trial showed that Tramadol was effective and safe in the treatment of pain of diabetic neuropathy.

Q. Why did this conclusion with respect to Tramadol, why was that important to you?

A. Because Tramadol and Tapentadol, as we just mentioned in the '130 patent, have very similar mechanisms of action in terms of its work in the neuroceptor, the opioid receptor and also the norepinephrine reuptake inhibition.

Q. Let's turn to slide 40 if we could, Ted.

Slide 40 references Hollingshead. Could you please explain to the Court what's significant about the Hollingshead reference in slide 40 which is DTX 916?

A. So Hollingshead is a Cochrane review. And a Cochrane review is essentially looking at all studies published between 1980 and 2005 on. And this examined the effect of Tramadol and neuropathic pain.

Q. And what is the Cochrane review?

A. So, Cochrane review looks at all the published studies. And from that body of literature they select, with a highly

selective grading system, the randomized controlled trials. And then do further analysis like lumps the randomized controlled trials together to come up with a conclusion as to what they think the analysis will be.

Q. Is Cochrane review a well-regarded journal in the field of medicine?

A. Yes.

Q. What was the conclusion presented in the Cochrane review DTX 916?

A. So, as of 2006 they concluded that Tramadol is an effective treatment for the neuropathic pain.

Q. Let's turn to slide 41.

Slide 41 references DTX 1141. What is illustrated in slide 41?

A. This is a study by Gilron, PTX 1141, published in 2005. It is a study where they compared patients with diabetic peripheral neuropathy and post herpetic neuralgia and they studied the effect in a randomized controlled treatment fashion.

Q. And what drugs were studied in PTX 1141?

A. They studied morphine which is an opioid. And also studied Gabapentin which is typically utilized as an anti-seizure drug and the combination of those. And the results were published in the New England Journal of Medicine which is considered to be one of the highly impactful journals

in the medical profession.

Q. What statements were made in PTX 1141 that informed your opinion in this case?

A. In the discussion they talk about, in addition to evaluating combination therapy, which is why the study was made, this trial replicates the evidence from previous studies of the efficacy of opioids in neuropathic pain.

Q. Let's turn, if we could, to slide 42. Slide 42 references DTX 1609.

Dr. Buvanendran, what is significant about the information contained in slide 42 which informed your opinion in this case?

A. So, this is algorithm treatment for this May of 2004. This is DTX 1609 by Namaka where they looked at what is the appropriate treatment that could be provided for patients with neuropathic pain.

Q. And what is a treatment algorithm?

A. You generally want to have a step like a three step wise treatment for the treatment of neuropathic pain. And this algorithm goes over the treatment modalities for the treatment of neuropathic pain.

Q. And why is that significant to your analysis?

A. Because we just, as we mentioned about you can see in this Table 3 of this excerpt talks about the opioids such as morphine, Methadone and Tramadol as utilized for the treatment

of neuropathic pain again in 2004.

Q. Okay. And did you look at other prior art references in connection with your understanding of the definition of this issue prior to 2007?

A. If I may just have the next slide because I put here a summary slide of the various literature that's available for the utilization of opioids for the treatment of neuropathic pain predating March 12, 2007.

Q. Okay. And on slide 43 there's a column that's headed Tramadol and the listing of articles.

What was significant about those articles that caused you to list them under the heading Tramadol?

A. So, these were all Tramadol, as I said, opioid or opioid like drugs. And it has, this is from June of 1998, the Harati article, DTX 1605; the July 2005 Freeman article talks about DTX 1603, December 2005; the Finnerup article, PTX 1131 and February 2006, the Baron article, DTX 1599, and July 2006 the Hollingshead article on DTX 916.

These all utilized Tramadol to demonstrate its efficacy for the treatment of neuropathic pain.

Q. Okay. And there's a column headed Oxycodone in references there. What do those references teach?

A. Oxycodone again is an opioid. And here again I put some literature that supports the evidence that Oxycodone is used for treatment of neuropathic pain in the July of 2005

Freeman article, DTX 1603; the Finnerup article in 2005, PTX 1131, and Baron's article in February of 2006 in DTX 1599.

Q. Okay. And there's a third column there listed as Methadone.

Why did you call that out to the Court?

A. Methadone is an opioid as well for the treatment of neuropathic pain. And I have two references now Namaka in 2004, DTX 1609, and in February of 2005, the Hays article, DTX 1606 talks about Methadone for the treatment of neuropathic pain.

Q. Okay. And pardon me, the last column is listed as morphine.

What do these articles say about morphine and polyneuropathic pain?

A. Morphine is an opioid as well for the treatment of neuropathic pain in November of 2003, the Dworkin article, DTX 1601; the Namaka article, DTX 1609 and the March article by Gilron that we just talked about, PTX 1141; the December 2005 the Finnerup article, PTX 1131 and the Baron article, DTX 1599.

Q. In conclusion, Dr. Buvanendran, all of those references predate March 12, 2007, the effective date of the '130 patent?

A. Yes.

Q. And do all of those references indicate that opioids were known to be effective to treat neuropathic pain?

A. Yes.

Q. Okay. Does the prior art literature about which you've testified also reflect your personal clinical practices in the 1990s and the 2000s?

A. Yes.

Q. How so?

A. I use opioids for the treatment of severe pain for the treatment of neuropathic and polyneuropathic pain.

Q. And, Dr. Buvanendran, did you hear Dr. Christoph, one of the named inventors of the '130 patent, testify in this trial?

A. I did listen to some of the cross-examination. I read the trial testimony.

Q. Okay. Did he testify about Grunenthal's internal documents that discussed some literature published prior to 2007 regarding the use of opioids to treat neuropathic pain?

A. I looked at some of the excerpts from the Grunenthal document and they also say that opioids are utilized for the treatment of neuropathic pain.

Q. Okay. As of 2007, do you believe that there was any debate as to whether opioid or opioid like drugs were effective in treating neuropathic pain, including polyneuropathic pain?

A. There was no debate as to the effectiveness of opioids and opioid like drugs for the treatment of neuropathic and polyneuropathic pain.

Q. Was there some debate or controversy about using

opioids for the treatment even though it was effective?

A. So as I said there is no debate as to the effectiveness of these opioids for the treatment of neuropathic and polyneuropathic pain. But, there was debate or controversy surrounding the side effect profile of these drugs.

This controversy continues to date, whether it is neuropathic pain or nociceptive pain, the adverse effects of opioids namely typically opioid abuse, tolerance development and other side effects.

So the debate still continues as to the side effect profile of this class of drugs.

Q. But is there any debate about whether the drugs actually are effective in alleviating pain?

A. There is no debate as to the effectiveness of the drugs.

Q. Now, let's turn to demonstrative 44. In summary, Dr. Buvanendran, as of March 2007, would a person of ordinary skill in the art conclude that the asserted claims of the '130 patent would have been obvious in view of claim 117 of the '593 patent based upon your understanding of the definition of the term "pain"?

A. Yes.

Q. And what if pain in claim 117 of the '593 patent were restricted to only nociceptive pain? Would a person of ordinary skill in the art be motivated to treat polyneuropathic

pain using Tapentadol hydrochloride?

A. Yes, because it was, there was a lot of abandoned literature demonstrating opioid utilization prior to 2007 for neuropathic pain.

Q. And under this circumstance, would a person of ordinary skill in the art have a reasonable expectation of success in alleviating polyneuropathic pain by administering Tapentadol hydrochloride?

A. Yes.

Q. So, if pain in claim 117 of the '593 patent were restricted only to nociceptive pain, would a person of ordinary skill in the art be motivated to treat polyneuropathic pain using Tapentadol hydrochloride?

A. Yes.

Q. And why is that?

A. Because I have demonstrated not only from all the clinical studies that their opioids were utilized for the treatment of polyneuropathic pain prior to 2007 with effectiveness, and again in my clinical practice I use opioids for the treatment of polyneuropathic pain and neuropathic pain.

Q. Would the same be true in connection with treating diabetic polyneuropathic pain and diabetic polyneuropathy by administering Tapentadol hydrochloride?

A. Yes.

Q. And as of March 2007 would a person of ordinary skill

have been motivated to test the efficacy of the Tapentadol used in an animal model of polyneuropathic pain?

A. Yes.

Q. And would the same be true for an animal model of diabetic polyneuropathic pain?

A. Yes.

Q. What would the results have been expected to be?

A. I would have expected it to be effective.

Q. Okay. Let's turn to a different topic, slide 45.

Dr. Buvanendran, did you consider secondary, a couple of secondary considerations as part of your obviousness analysis?

A. Yes, I have put up some legal standards.

Q. Before you go there, what secondary considerations did you consider?

A. I considered the unexpected results and the long felt needs.

Q. Now, turning to slide 45, is that your understanding of the legal standards or the legal tests for unexpected results and long felt need?

A. Yes. As I say, I'm not a lawyer. But, this is what I was informed the claim invention must achieve, a superior property or advantage, and over the closest prior art, and that a person of ordinary skill would not have expected it.

Q. Okay. And what is your understanding of the legal

standards governing long felt need?

A. At the time of the patent somebody must have a persistent and recognized need for, need by the person of ordinary skill in the art, must not be satisfied by any other solution, and the claimed invention must satisfy the long felt need.

Q. Now, let's go back and look at unexpected results.

In your opinion, did the evidence presented that you've seen so far presented by plaintiffs show that the claims of the '130 patent demonstrated an unexpected result?

A. As I said before, I have a demonstrative of the various opioids that have been utilized for the treatment of a neuropathic pain.

Q. Okay. I think I might have missed the answer.

Did you consider the question?

A. Yes, I did.

Q. And what is your opinion as to whether the evidence demonstrates that the claims of the '130 patent demonstrated an unexpected result?

A. We did not -- it did not provide an unexpected result.

Q. Okay. Let's, if we could, please turn to the slide.

What was the superior property that plaintiffs claim is present in the claims of the '130 patent?

A. The superior property that the plaintiffs claim is that it is an opioid treatment for the neuropathic pain. And the

second point they made was that it has decreased adverse effects of the side effects.

Q. What is the closest prior art to Tapentadol, in your opinion?

A. The closest prior art I would consider would be Tramadol.

Q. Why is that?

A. Well, Tramadol, like Tapentadol, has similar mechanisms of action. Both drugs work as the MU receptor or the opioid like receptor. And they are, both of the drugs also have inhibition of the descending pathway, the norepinephrine inhibition.

So when the pain signals come down from the brain down, it inhibits the norepinephrine reuptake mechanism and they, both drugs, provide this method of action to provide pain relief.

Q. And did plaintiffs produce any evidence that Tapentadol is superior to Tramadol for the treatment of polyneuropathic pain?

A. No.

Q. Did plaintiffs present evidence that Tapentadol is superior to Tramadol as it relates to side effects?

A. No.

Q. And was it unexpected in 2007 that an opioid like Tapentadol would be effective in treating polyneuropathic pain?

A. It was expected that a drug of this nature would provide pain relief.

Q. And what is the basis for your opinion in that regard?

A. As I said before, the Tramadol has a very similar mechanism of action and Tapentadol -- Tramadol does provide pain relief for the neuropathic and polyneuropathic pain patients and I would expect Tapentadol to do the same.

Q. And let's turn to slide 46.

Is slide 46 a list of references that you've already been through and told the Court that indicate that those would be expected to be effective, that these particular opioids were effective in treating polyneuropathic pain?

A. I list in this slide all the opioid and opioid like drugs for the treatment that has been available back in 2000, prior to 2007, March.

Q. Now, let's turn to the topic of long felt need. Put up slide 47, please.

Now, in your opinion, doctor, was there a long felt need for Tapentadol in 2007?

A. In 2007 there is no long felt need.

Q. What is the basis for your opinion?

A. So, in this slide I put up here the various categories of drugs that have been available in 2007 for the treatment of neuropathic pain.

In the left-hand column you will see the

antidepressants which are the tricyclic antidepressants that are typically utilized such as amitriptyline and nortriptyline, and some of the other classes of drugs such as SSNRIs and the antiepileptics such as gabapentinoids and the pregabalins and the other sodium antiepileptics which have always been utilized for treatment of neuropathic and polyneuropathic pain.

Q. What is the source for the information that you've listed on slide 47?

A. So, this excerpt is from the Baron article, DTX 1599.

Q. And what were considered first line treatments, treatment options in 2007 for the treatment of polyneuropathic pain?

A. Pretty much all the drugs that I have just talked about, the antidepressants, the antiepileptics, both the sodium and calcium channel blockers were all considered first line treatment for the treatment of neuropathic pain.

Q. Were opioids the first line treatment for polyneuropathic pain in 2007?

A. No, they were not first line treatment then in 2007.

Q. What line treatment were they?

A. They were the second line treatment and they are second line treatment as of now currently as well.

Q. Okay. So were the first line treatments back in 2007 are still first line treatments today?

A. Yes.

Q. And were the second line treatments back in 2007 still second line treatments today?

A. Yes.

Q. So, how is Tapentadol used today for the treatment of polyneuropathic pain?

A. Tapentadol is a second line treatment for the treatment of neuropathic pain.

Q. So, in your opinion has Tapentadol met a need for a new treatment for polyneuropathic pain?

A. No.

Q. Did plaintiffs identify any other need that Tapentadol allegedly filled?

A. As I said before, the plaintiffs allege that maybe Tapentadol could have decreased side effects or adverse effects of abuse potential.

Q. And did Tapentadol meet that need?

A. No.

Q. And why do you say that?

A. Well, because I have a demonstrative for that, if I may have the next slide, please.

Essentially the DEA classifies opioids into the various schedule drugs depending on their abuse potential. It goes from a Schedule 1 to Schedule 4. The Schedule 1 being the most abused. And you have in this class heroin and cocaine as Schedule 1 drugs.

Q. Okay. Where does Tramadol fit on that schedule?
A. Tramadol was, in 2007, an unscheduled drug.
Q. And where does Tapentadol fit on that schedule?
A. Tapentadol was categorized as Schedule 2 in 2007.
Q. By the way, Dr. Buvanendran, what data are considered when DEA places drugs into the schedule?
A. They examine their abuse potential from clinical studies.
Q. And what does it mean for two drugs to be in the same schedule for the DEA schedule?
A. So, essentially it would be that they are the same abuse potential. And in this case Tapentadol is a Schedule 2, it would be in the same category as morphine, Oxycodone, Fentanyl.
Q. And I think you testified that in 2007 Tramadol was an unscheduled drug?
A. That is correct.
Q. And what did that say about its perception of abuse potential in 2007?
A. In 2007 it was believed that it was of low potential for abuse.
Q. Now, Dr. Buvanendran, in summary, do you believe that a person of skill in the art in March 2007 would have considered claims 1, 2, 3 and 6, obvious in view of claim 117 of the '593 patent?

A. Yes.
Q. Okay.
MR. CONNOLLY: Your Honor, I need to consult with my colleagues for one second. And I believe I will either have another few seconds or other options. Dr. Capuano has a short examination.
THE COURT: That's fine. Do you want to take a moment?
MR. CONNOLLY: Thank you very much, Dr. Buvanendran. At this time I have no further questions. I turn the floor over to Dr. Capuano for Actavis.
THE COURT: Thank you very much.
CROSS EXAMINATION BY MR. CAPUANO:
MR. CAPUANO: Your Honor, I just have a few slides. Maybe ten minutes on that issue.
THE COURT: That's fine. Go ahead.
MR. CAPUANO: Separate from the issues we heard about before.
Q. Good morning, Dr. Buvanendran.
A. Good morning.
Q. Dr. Buvanendran, do you have an opinion regarding whether claims 1 and 2 of the '130 patent are invalid because they are anticipated by the prior art?
A. Yes.
Q. And do your demonstrative exhibits include a section to

help you explain those opinions?

A. Yes, I have a demonstrative on the legal standards of anticipation.

Q. And you testified you aren't a lawyer. But, nevertheless, do you have an understanding of what's required to show that a patent is invalid as anticipated?

A. Yes.

Q. Okay. And what is your understanding of that requirement?

A. So, single prior art reference discloses each limitation of the claim, either expressly or inherently.

Q. Okay. And you have the word "inherently" here.

Do you have an understanding of what it means for something to be disclosed inherently?

A. Yes, a claim limitation is inherent if the subject matter described in the reference necessarily functions in accordance with or includes the claimed limitations.

Q. And in arriving at your opinions regarding anticipation, did you apply these principles as you understand them?

A. Yes, I did.

Q. Dr. Buvanendran, you recognize what's on the screen here as defendant's Exhibit 752?

A. Yes.

Q. And what is defendant's Exhibit 752?

A. This is DTX 752 is the patent, '737 claim patent.
Q. Okay. And do you have an understanding of the date on which this patent was granted?
A. I believe this was granted in 2011 sorry, 2001.
Q. Thank you. And does the '737 patent describe Tapentadol hydrochloride?
A. Yes.
Q. And is that description here in the structure of example 25 of the '737 patent?
A. Yes.
Q. And what are the uses for Tapentadol hydrochloride that are described in the '737 patent?
A. It talks about the underlying object of the present invention was to provide substances with an analgesic effect, which are suitable for the treatment of severe pain without giving rise to the side effects.
Q. So, at column one of 752, of defendant's Exhibit 752, the '737 patent at lines 52 to 55, is that what you are referencing here in demonstrative Exhibit 53?
A. Yes.
Q. And does the '737 patent describe a method of administering Tapentadol hydrochloride as an analgesic to the population suffering from severe pain?
A. Yes, it does.
Q. Okay. And you've put together a demonstrative which is

demonstrative Number 54.

What are you showing here in this demonstrative, Dr. Buvanendran?

A. I'm showing here this large population of patients with severe pain in the outer circle. And in that outer circle there's the smaller subpopulation of patients with patients with polyneuropathic pain as stated in the claim, patent '130.

Q. And is this relationship between the larger population of severe pain, those suffering from severe pain, and the subpopulation with polyneuropathic pain that you've indicated here, is that consistent with your experience in diagnosing and treating patients with severe pain?

A. Yes.

Q. Now, Dr. Buvanendran, is this Venn diagram, is this diagram that you included in slide 54, is this printed in the '737 patent?

A. No, it's not.

Q. Is the word polyneuropathic pain or polyneuropathy, is that word specifically used in the '737 patent?

A. No, it's not.

Q. Without those words being in the '737 patent, how is it that this subpopulation that you've included here on demonstrative Exhibit 54 is within the larger population of severe pain sufferers?

A. I know that because I mean this is a large population

of patients with severe pain. And as I mentioned all this time, this is a subpopulation of patients with severe pain who have polyneuropathic pain.

Q. Okay. And if a physician were to practice the method of administering Tapentadol as an analgesic to the population of those suffering from severe pain as described in the '737 patent, would that method necessarily include treating that subpopulation suffering from severe polyneuropathic pain?

A. Yes.

Q. Dr. Buvanendran, is the method of the '737 patent a method of administering Tapentadol hydrochloride?

A. Yes.

Q. And is that the same as the method of administering Tapentadol hydrochloride part of claims 1 and 2 of the '130 patent?

A. Yes, it is.

Q. And as you have here on demonstrative Exhibit 56, is the method of the '737 patent directed to treating a population of patients with severe pain?

A. Yes.

Q. And is the population of the claims 1 and 2 of the '130 patent addressing that subpopulation with polyneuropathic pain?

A. Yes.

Q. And do you believe that claims 1 and 2 of the '130 patent are inherently anticipated by the method described in

the '737 patent?

A. Yes, I do.

MR. CAPUANO: I have no further questions, your Honor.

THE COURT: Thank you. All right. I think why don't we take our break at this point. Does that sound good?

MR. SITZMAN: Yes, your Honor, that sounds good.

THE COURT: Let's take about 5, 10 minutes for our break. I remind the witness that you are under oath. You are not to speak to Counsel about your testimony.

We are going to take about a ten-minute break. So you can step down from the stand.

THE WITNESS: Thank you.

THE COURT: Thank you very much.

(Whereupon a short recess was taken.)

THE COURT: All right. Everyone, have a seat. Let us start plaintiff's cross of the witness.

Any issues on the exhibits?

MR. CAPUANO: Nothing so far, your Honor.

MR. CONNOLLY: No, your Honor.

CROSS EXAMINATION BY MR. SITZMAN:

Q. Dr. Buvanendran, I would like to start by picking up where I think you left off with the defendants.

It's your testimony that Tapentadol did not provide any unexpected results, correct?

A. Yes.
Q. And it's your testimony that it didn't satisfy the long felt need, right?
A. Yes.
Q. And it didn't, Tapentadol didn't provide any reduction in side effects.
That's part of your long felt need analysis, correct?
A. That is correct.
Q. And it did not provide any synergistic results as part of your unexpected results theory?
A. Right. I'm not sure what you mean by synergistic results.
Q. More than additive, right? There's no synergy about Tapentadol, right, according to you?
A. I don't think I used the word "synergy" so I am not sure. If you can clarify that word for me.
Q. Okay. I'm going to use the word "synergy".
Do you believe that Tapentadol is synergistic in its use?
A. Sorry, I would happy to answer. You say the synergistic use with what? I'm not sure in terms of what?
Q. Do you know what the word "synergy" means?
A. Yes.
Q. What is your definition of synergy?
A. Synergy means addition or additive.

Q. Isn't it more than additive, doctor? Isn't the word "additive", additive and the word "synergy" more than additive?

A. You could say that.

Q. Do you believe Tapentadol is synergistic in its behavior?

A. I mean if you're talking about the mechanism of action or are you talking about the disease conditions that it treats?

Q. I'm talking about the way it behaves inside the human body as you're treating patients.

A. I'm sorry, I didn't really understand the question.

Yes, it does work in dual methods of action. It has, as I said, it has the MU receptor and it also inhibits the norepinephrine reuptake inhibition. So, it does have a dual mode of action.

Q. So, again do you consider Tapentadol to be synergistic in its behavior?

A. As a drug as it works, it does.

Q. That's a yes?

A. Yes.

Q. Okay. All right. I'd like to look at a few of the slides that your Counsel showed you. And let's start with slide 17 of the defendant's demonstratives.

MR. CONNOLLY: Your Honor, I think we are getting into confidential labeling information. I ask that the courtroom be closed.

THE COURT: Yes. Any issue? Anyone have any issue with sealing? Counsel?

MR. SITZMAN: Sorry, none from me.

THE COURT: Let us seal the courtroom.

(Whereupon the hearing was sealed).

(Whereupon the following takes place in open court)

Q. Doctor, I was asking you about the '737 patent.

Can we agree that the treatment of polyneuropathic pain is not disclosed in this patent either?

A. That's correct.

Q. And the treatment of polyneuropathic pain with Tapentadol is not disclosed in this patent, correct?

A. That's correct.

Q. And you'll agree with me that severe pain is not necessarily polyneuropathic pain, correct?

A. I mean we talked about it before. I mean patients with severe pain may have polyneuropathy.

Q. But, you just got done telling me on your list about these patients who have obstructed ureters and kidneys and either you treat them, I assume, those pains are severe, right?

A. Yes.

Q. And those are not polyneuropathic, correct?

A. That's correct.

Q. So my question to you is can you agree with me that

severe pain is not necessarily polyneuropathic?

A. It's not all polyneuropathic.

Q. Now, could we jump ahead to Page 17146? And can you bring up the pharmacological investigation?

Now, doctor --

A. Sorry. Okay. I'm sorry.

Q. Now, doctor, the patent includes a number of examples of synthetic chemical methods, right?

A. Yes.

Q. Okay. And then it ends with this pharmacological investigation, correct?

A. Yes.

Q. Okay. And this reports on the writhing test on mice?

A. Yes, that's what it says.

Q. Okay. And the writhing test in mice, that's a nociceptive pain test?

A. I think I believe we talked about it at deposition as well. So, you know, even though I do a lot of animal models, a writhing test is not one of the models that I have done in our laboratory. And so I do not want to comment on something that I don't do in the laboratory in our practice.

Q. But I thought you held yourself out, doctor, when Mr. Connolly put up your definition of a POSA, a person of ordinary skill in the art, you said that that person needed to have animal study experience, right?

A. That's correct.

Q. And do you have animal model experience?

A. Yes, I do, because I normally have done animal models in our lab that we have. But I have created my own animal models.

Q. And you have no experience with the writhing test on mice and you can't offer an opinion in this court as to whether that's nociceptive?

A. As I have said we have not done it. In my last 15 years in the lab, I have not done writhing tests. And I have said that in the deposition as well when we met in Chicago.

Q. Have you ever read anything about the writhing test?

A. I mean I have read about it but I have not done it. And so the only thing I would say that it isn't all the tests that is not commonly done nowadays. And so, I really can't comment too much about it. But, it is considered probably more nociceptive than neuropathic.

Q. It is nociceptive, right? Isn't that what's being tested here in the phenylquinone mice?

A. Again, as I said, I am not an expert on this specific test, the writhing test, because I have not done it. I can only tell you what it would probably indicate.

Q. Do you recognize this mouse model as a recognized neuropathic model?

A. I don't think so because I have reviewed the literature on neuropathic pain and we are very much in the neuropathic literature testing for rats at the time.

Q. Now, I want to confirm your understanding of what's required for anticipation.

You understand that for a reference to anticipate a patent, the reference must explicitly or necessarily disclose each element of the claims, correct?

A. Correct. I believe that's the legal standard. But let me pull up the slide.

Q. Correct?

A. Yes. I think, can you just repeat the question? I'm sorry. I was just trying to pull up the slide.

Q. Sure. You understand that for a reference to anticipate the claims of a patent, the reference must explicitly or necessarily disclose each element of the claim?

A. That's true.

Q. And in this case the essential elements of the '130 patent are claims for the treatment of polyneuropathic pain with Tapentadol, correct?

A. Correct.

Q. So, the '737 patent does not explicitly or necessarily disclose polyneuropathic pain or the treatment with polyneuropathic pain including Tapentadol, correct?

A. It does not.

Q. Now, for your obvious type double patenting opinion, you're relying on claim 117, correct?

A. Correct.

Q. Okay. Can you show me where in the patent you have in front of you where claim 117 is?

A. It's on the '593 patent. I'm not sure if it's DTX.

Q. You have in front of you DTX 752.

And my question is, where in DTX 752 is the 117, claim 117?

A. Sorry. It's been awhile since I looked at it.

Q. So, doctor --

A. Yes.

Q. -- the '737 patent does not have claim 117 in it, correct?

A. I cannot find it right here.

Q. Can we go to the claims, Rob, at the back end of this exhibit? Last page, sorry.

Doesn't this patent end with Claim 8, doctor? Column 26, Claim 8?

A. Yes.

Q. Right. This patent ends with Claim 8, correct?

A. Correct.

Q. All right. Let's look at the '593 patent.

Can we have DTX 1346, please?

A. Sorry. Which DTX?

Q. Oh, sure, 1346.

If you look at the claims here, do you see claim 117 here?

A. Yes, this is column 38.

Q. Column 38. Okay. Can we stay here for a second, though, Rob?

A. Sorry.

Q. What is the date of issuance of the '593 patent?

A. The '593 patent I think was issued in the priority date was July 23, 1994.

Q. That's not what I asked. I asked when did it issue.

A. The date of reissue of the patent was April 24, 2007.

Q. Okay. Good. Let's look at the '130 patent, the patent you claimed as obvious in light of claim 117.

Can we pull up DTX 75? What's the priority date, the provisional application date of this patent?

A. The date of the patent was September 17, 2013 and the the priority publication date was December 9, 2010.

Q. Now, you see the provisional application right below that.

When was the provisional application filed?

A. It was filed in March 12, 2007.

Q. That's before the '593 patent issued, correct?

A. Correct.

Q. So, to confirm, you're relying on a claim, claim 117,

that did not exist when the '130 patent was filed, correct?

A. I believe the '593 patent was the refile date that you made me read on top.

Q. Right. And that reissue date when the 117 came into existence was after the date that the '130 patent was filed, correct?

A. It's my understanding the '593 was back in 1994 and that the '130 is in 2007.

Q. Okay. I'm going to ask again.

When the '593 issued for the first time with claim 117 in it, it was after the date, the priority date of the 130 patent, correct?

A. That's correct.

Q. You will agree with me, doctor, that Tapentadol was the first opioid to be approved by the FDA to treat polyneuropathic pain right?

A. Yes.

Q. And when was it first publicly disclosed or known that Tapentadol had MU opioid activity?

A. I can't tell you the exact date. I was known that it had MU activity. But it was known that Tapentadol had activity of the mu receptor and the norepinephrine reuptake inhibition.

Q. So, when was it known, publicly known, that it had the MU opioid receptor activity? Or is it your testimony that both mechanisms of action were publicly disclosed on the same day?

A. I believe they were disclosed at the same time that it had the MU activity and the norepinephrine reuptake inhibition.

Q. And when was that?

A. I want to say it's probably around 2006.

Q. Okay. Can you recall what reference it was that it was disclosed in?

A. I cannot recollect exactly the specific reference that it was disclosed in.

Q. Do you remember the author's name? Tzchentke? Can you remember that?

A. Yes.

Q. Is that the reference you are referring to as the disclosure of the MU opioid activity and the norepinephrine reuptake inhibition?

A. That's correct.

Q. Okay. Now, back when the '737 patent issued, without the claim 117 then, practitioners were not using opioids as first line treatment for the treatment of polyneuropathic pain, correct?

A. I believe in -- no, it was not used then and it is still not used.

Q. Okay. And you'd agree with me at that time that the effectiveness of opioids in treating polyneuropathic pain was controversial, correct?

A. No. As I said before, the efficacy of the utilization

of opioids for the treatment of neuropathic pain was not the area of controversy. The area of controversy, as I said, was the adverse advanced effects of the opioids in terms of tolerance and abuse potential.

Q. All right. Let's take a look at some of those articles then. Let's start with Namaka. It's DTX 1609.

A. Is that in your binder or the previous binder?

Q. You can use our binder. I think it's in there.

This is one of the articles you relied on, correct?

A. Yes.

Q. This is one of the articles you relied on to say that it was obvious to try Tapentadol to treat polyneuropathic pain, correct?

A. Yes.

Q. Okay. By the way, does Namaka refer specifically to polyneuropathic pain?

A. I believe he talks about neuropathic pain.

Q. Not polyneuropathic pain? It just talks about neuropathic pain, correct?

A. Correct.

Q. And Namaka was published in 2004?

A. That's correct.

Q. Let me turn your attention to Page 13760 and let me have you pull up right where you are, Rob. Thanks.

It says at the top beginning with the usefulness of

narcotics, which is where opioids would fall into, correct, doctor?

A. Yes.

Q. The usefulness of narcotics in the treatment of chronic neuropathic pain is often debated and not very well studied.

Do you see that?

A. Yes.

Q. Do you disagree with Namaka on this?

A. No, I'm saying that it is what it says, the usefulness of narcotics in the treatment of chronic neuropathic pain is debated. And there are some studies, but there are some studies that are not showing efficacy. There are some studies to that effect.

Q. All right. And in fact Namaka says down starting with as, it says As there is limited assessments of opioid effectiveness in neuropathic pain, they should not be considered as a first line treatment, right?

A. Yes, it was then in 2004 it was not a first line treatment and it is still not a first line treatment in 2016.

Q. And here they are talking about the limited assessments of opioid effectiveness, correct?

A. Correct.

Q. And despite what Namaka has to say now you are still of the opinion that a physician would have been motivated to use Tapentadol to treat polyneuropathic pain despite this

information?

A. In the article as I stated before they had several opioids, morphine, Methadone, Tramadol and opioid and opioid like drugs listed in their table of contents demonstrating that these drugs would be used for, and again it is not for first line treatment, but again used as a second line treatment back in 2004 and in 2016.

Q. I think you may have missed my question.

Despite what Namaka has to say, is it your opinion that a physician would have, nonetheless, been motivated to use Tapentadol to treat polyneuropathic pain?

A. Yes.

Q. And would a person of ordinary skill in the art reasonably predict that Tapentadol would be effective in treating polyneuropathic pain?

A. Yes.

Q. Notwithstanding these statements?

A. That's correct.

Q. Okay. Let's turn to Baron, DTX 1599.

This is another article that you rely on, correct?

A. Yes, I did talk about it.

Q. Okay. Same question here, does Baron specifically refer to polyneuropathic pain?

A. I believe it's an article on neuropathic pain.

Q. But not polyneuropathic, correct?

A. Correct.

Q. Okay. Let me have you turn to Page 13663. And in the paragraph on analgesics starting with the sentence that says however, it's up here, Rob.

It says However, in contrast to widespread opinion, neuropathic pain has been shown to be opioid sensitive. Do you see that?

A. Yes.

Q. And you see the widespread opinion, correct?

A. I do.

Q. Okay. You don't agree with the wide spread opinion, do you?

A. I am saying that when it says that it is useful for the treatment of neuropathic pain and it was known and it is useful and I was prescribing opioids back in 2004 for the treatment of pure neuropathic pain.

Q. All right. And despite the wide spread opinion, you believe that a person of ordinary skill in the art back with the Baron article in front of them, would nonetheless prescribe Tapentadol for the treatment of polyneuropathic pain?

A. Yes.

Q. And it's also your testimony that despite widespread opinion, that the person of ordinary skill in the art would have predicted success with using Tapentadol for the treatment of polyneuropathic pain?

A. Yes.

Q. Okay. Let's look at another one. Can I have DTX 1401?

There is an article by Dworkin. Let me start by asking you if you recognize this article.

A. This is the 2007 article by Dworkin and I may have skimmed it in my regular review of stuff.

Q. Exactly. So you relied on the Dworkin article from 2003, right?

A. I did review that before. But again I reviewed so much literature, I can't recollect exactly, but approximately, correct.

Q. And you know that Dworkin, between his 2003 article and this article, changed his opinion as to whether opioids would be effective in treating neuropathic pain, right?

A. I haven't look at this article specifically but I would be more than happy to look at it if you show it to me.

Q. I will show you a couple of pages. But generally do you know that to be the case, that Dworkin changed his opinion from 2003 to 2007?

A. No.

Q. Okay. Let's look at what's been Bates stamped in the corner as 764 in the introduction, second paragraph, the management of patients.

A. Sorry, so which page did you say?

Q. It's the article, it's page, it's the second page of

the article under introduction in the bottom corner. It's Bates stamped 764. And the leadoff there says the management of patients with chronic N.P., neuropathic pain, is complex and responsive to existing treatments is often inadequate.

Even with well-established neuropathic medications, effectiveness is unpredictable, dosing can be complicated, analgesic onset is delayed and side effects are common.

Do you see that?

A. Yes.

Q. Do you disagree with Dworkin in 2007?

A. It is true then, it is still true that even with well established pain medications, neuropathic pain is a challenge to treat.

Q. Let's turn a little bit forward in the article to Page 9 of the article, Bates stamped 771 in the bottom right. Thanks Rob.

First column begins with the word "because". Because of these problematic aspects of opioid treatment and given the efficacy of first line medications discussed above, treatment of chronic, N.P., neuropathic pain, with opioid agonists should generally be reserved for patients who have failed to respond to or cannot tolerate the first line medications.

Do you see that?

A. Yes.

Q. Despite these statements in Dworkin which is a change

from 2003, you still believe that a person of ordinary skill in the art would have prescribed Tapentadol for the treatment of polyneuropathic pain, correct, doctor?

A. I believe it says that it should not be used as a first line treatment. And I have said this several, several times, that it is not a first line treatment prior. It is not a first line treatment now. And it was not a first line treatment in 2007.

Q. Doctor, in 2007 would a person of ordinary skill in the art have prescribed Tapentadol for the treatment of polyneuropathic pain?

A. As a second line treatment.

Q. So, is that a no or is that a yes or you're now changing kind of what your overall opinion is?

A. I have not changed my opinion. And I said exactly the same thing since this morning and in my depositions. It is a treatment for neuropathic pain but it is not the first line treatment for neuropathic pain.

Q. So, it's not the first drug. It's not even in the first category of drugs that a person of ordinary skill in the art would have considered, correct?

A. Correct. It's not the first line of therapy for the treatment of neuropathic pain.

Q. Okay. Is there anything -- well, let me ask you this same question as I asked before, would a person of ordinary

skill in the art have had an expectation of success with Tapentadol for the treatment of polyneuropathic pain?

A. Yes, because opioids have been shown by the Gilron article, which is very highly cited. They are a respected journal, The New England Journal of Medicine, that demonstrates opioid which in this case is morphine, to be effective in two models of neuropathic pain.

Q. Okay. Let's keep looking.

Can I have the next exhibit PTX 3002? Let me ask if you recognize this article from 2011?

A. I believe the first time I saw it was at the deposition but --

Q. You know Dr. Candiotti?

A. I actually do.

Q. What's that?

A. I do.

Q. Let's turn to Page 2 of the article. The bottom. Thank you.

It reads "Among the pharmacological or the pharmacologic approaches, the use of opioids for the treatment of noncancer pain is particularly controversial".

Doctor, is it still your opinion that there was no controversy regarding the use of opioids to treat noncancer pain or neuropathic pain?

A. As I said in terms of efficacy, there has been efficacy

data demonstrating it. And we have all used it as clinicians for the treatment of pain.

The controversy still surrounds the utilization of opioids and the adverse effects that these drugs do cause.

Q. So, this controversy here, you're redefining this controversy as not about effectiveness, despite all the articles we saw, you're redefining this controversy in terms of side effects.

Is that what I'm understanding?

A. So, when you treat a patient with a drug, with any compound for any disease condition, you outweigh the risk and the benefits. And so when there is risk and benefits, it's an area of controversy if a drug does not cause any side effects and it's obviously beneficial.

But when you have a risk/benefit ratio, it is important as a clinician to weigh the risk and benefits and therefore there will be areas of controversy.

Q. Okay. So we can at least agree, even though we may have a different characterization of what the controversy is, we can agree that the use of opioids for the treatment of neuropathic pain was controversial just like Dr. Candiotti said?

A. So, what I would agree is that the effectiveness of opioids for treatment is not the area of controversy but more on the risk/benefit risk is an area of controversy before and

it still continues in 2016.

Q. All right. Let's move on to a paper that I think you will recognize, Exhibit 3003.

Doctor, this is your paper, right? This is your name on the back here?

A. Yes. So, this was a paper written by one of the people I trained, Dalia Elmofty is one of the students that I taught.

Q. So you wrote this paper in 2013, correct?

A. Well, she wrote it, yeah.

Q. I'm sorry, so do you disavow what's in the article? Is that what I'm hearing?

A. No, my name is there.

Q. Let's look at Page 479 under opioids. And doctor, the first sentence, "the use of opioids for the treatment of neuropathic pain remains controversial".

We're now up to 2013. We've seen articles that go all the way back to the '90s, 2004, this controversy this dispute has continued, correct?

A. As I said before, the controversy still continues. It is not about the effectiveness, it's about the adverse effects that opioids do. And it's a risk I take everyday when I prescribe opioids to patients. Actually now it is nociceptive or neuropathic pain, except cancer patients.

Q. So, if I understand what you're saying, there is no dispute in your mind that the long term benefit for using

opioids for the treatment of neuropathic pain was clear and undisputed?

A. I do not believe that's what I said. I said the effectiveness of the use of opioids for neuropathic pain is not disputed. However, I said when you give drugs to a patient, there are side effects and we need to weigh the side effects and the benefit of that to that particular individual to this disease condition.

Q. Despite the controversy, despite the statements we've seen so far, you still believe a person of ordinary skill in the art would have prescribed Tapentadol for the treatment of polyneuropathic pain?

A. Yes.

Q. And you would have expected the person of ordinary, or you would have, your opinion is that the person of ordinary skill in the art would have expected success with Tapentadol for the treatment of polyneuropathic pain?

A. Yes. I would have expected it to work like any other opioid.

Q. Okay. All right. Doctor, let's look at something that just came out last week. It's in your book at PTX 3004.

Do you recognize this document?

A. I recognize the document but I have reviewed it awhile ago. I mean I've reviewed it.

Q. I'm sorry, this just came out March 18th. And I

thought you testified on direct that you were part of the CDC group that provided the information and guidelines that are set forth in this document. Isn't that true?

A. What I testified to the fact was that the CDC formatted its guidelines. And various societies, including patient groups were invited to make a comment. I was the representative from the 55,000 members of the American Society of Anesthesiologists to review and to comment, solely provide comments to the CDC. Finally the ultimate product was the CDC's output.

Q. So you had some involvement in what ultimately we're seeing here as the final output, correct?

A. Let me correct that again. I did provide input but I had no control over the output of the product.

Q. Were you the only one who provided input or were there professionals from around the world in all sorts of disciplines that provided input?

A. So, I'm not sure the world. I think it was restricted to the U.S. I believe they invited a lot of pain societies. Probably they invited some pain societies and some patient groups, the American Medical Association and the American Society of Anesthesiologists who were invited to provide comments including the H.S.S., the Human Health circuitry.

Q. Let's take a look at a few of the things inside here. Page 3, the bottom of the first column. Thanks Rob. And then

continuing up on the next column.

The article reads, "Although the transition from use of opioid therapy for acute pain to use for chronic pain is hard to predict and identify, the guideline is intended to inform clinicians who are considering prescribing opioid pain medication for painful conditions that can or have become chronic".

Do you see that?

A. I'm really sorry. I was reading. Is this Page 3? I'm sorry.

Q. That's okay. It's at the bottom of the first column and the top of the second column.

A. Is that the column starting with The recommendation?

Q. It says Scope and audience.

A. Okay. I'm sorry.

Q. This is consistent with what you understood these guidelines to be when they were soliciting information, correct?

A. Yes, that's what it says as you read. I'm not sure what the question is. Sorry.

Q. I just asked if that was consistent with your knowledge as to what the scope and audience was in terms of the purpose for this guideline.

THE COURT: Hold on.

MR. CONNOLLY: Your Honor, I just want to note

this is a new document. It wasn't put on anybody's exhibit list. It's supposed to be shown to him for impeachment. It's a 2016 document.

THE COURT: Although I think Mr. Sitzman exchanged the documents to begin the examination. No?

MR. SITZMAN: Yes.

MR. CONNOLLY: We got it now but it's not on any exhibit list. It's 2016. It's a document that's three days old. It has nothing to do with a person of ordinary skill's knowledge in 2007. He can't be -- he's not being impeached. He hasn't seen it. There's really no purpose for the examination other than to talk about a document that apparently came out three days ago. It's utterly irrelevant. It wasn't gone into on direct. And he talked about a person of skill's state of mind in March of 2007.

What the CDC is saying to doctors today has absolutely no connection to that whatsoever. We are talking about a document that was issued three days ago, your Honor. This is colossal waste of time.

THE COURT: He can let me know but I think he is using it for impeachment because of his connection with the CDC, is he not?

MR. SITZMAN: Correct. And also the fact that the doctor testified on direct that there is no question and no doubt through all of these articles that people, people of

ordinary skill in the art, would be prescribing opioids for the treatment of polyneuropathic pain.

MR. CONNOLLY: Your Honor, his testimony on direct was that at the critical date with respect to the '130 patent the state of literature before March of 2007 was that a person of ordinary skill in the art would have an expectation that an opioid product would work. That was his testimony.

He didn't give testimony about the relevance of a person of ordinary skill's knowledge today. This is all about a legal issue that is irrelevant. And the fact that he happens to have participated in the input and not the output of a document that is 7, 8, 9 years after the relevant period at issue, doesn't connect it up. It's utterly irrelevant to the topic.

THE COURT: Is there a response?

MR. SITZMAN: It is relevant. It goes to the heart of his opinions here. He louted this participation during his direct examination as to his participation, I am entitled to go into this. If they think it's irrelevant, then they will either brief it or on redirect they will do --

THE COURT: You can certainly respond to it. This has been the line of testimony. And this is the most recent document that we are discussing. And again in addition to there is the relationship with the CDC. I think based upon the entirety of that, you can go forward with the questioning.

MR. SITZMAN: Thank you, your Honor.

THE COURT: Thank you.

Q. Can we turn to Page 15 of the article?

A. I thought it would appear in the scope and audience of this.

Q. We were just going to move ahead now.

A. Okay. Sorry. Which page?

Q. Page 15, bottom corner.

Doctor, it says in summary --

A. Sorry, before you go, is it on the right hand or the left-hand column?

Q. The right hand.

A. The right hand column.

Q. In summary, the categorization of recommendations was based on the following assessment: Number 1, no evidence shows a long term benefit of opioids in pain and function versus no opioids for chronic pain with outcomes examined at least one year later.

Do you see that?

A. I see it on your slide but I still can't find the document here because I think I'm lost.

Q. It's at the bottom of Page 15 in the far right corner.

A. Oh, I'm sorry. I see it. Okay.

Q. Doctor, just this last week the CDC issued this opinion, for which you provided input, concluding there was no

evidence of long term benefit of opioids.

And yet you've testified in this case that as far back as 2007 or even earlier, according to some of the prior art that Mr. Connolly elicited, that there was no doubt in anybody's mind that opioids can be and should be used for chronic pain. How do you reconcile that?

A. Okay. I can tell you because essentially opioids were used in the '90s, 2000s and it continues to be used in terms for patients with severe pain.

There were several literatures that emerged with respect to adverse effects. We talked about it in terms of side effects. And when they started looking at the outcome in terms of one year or 6 months and now they moved it to one year, it demonstrated that the risk was more than the benefit that there was with this opioid treatment. And therefore that is what the guidelines say.

Now, let me finish because the guidelines also go on to say what should be prescribed for these patients with noncancer pain patients severe in nature and there were 12 recommendations set forth in this guidelines . The analysis was about risk/benefit ratio of the opioid treatment for these patients.

Q. Doctor, wouldn't a person of ordinary skill in the art consider all of the references that we've talked about, consider all of the controversy, consider all of the evidence,

consider everything that has been said and have some reasonable expectation that Tapentadol would work to cure or to treat polyneuropathic pain?

A. As I said before, it will be effective in the treatment of polyneuropathic pain. But, again, it will be associated with the risk. And these guidelines point to the risk. And in fact the guidelines go further on to talk about what dosage it should be started on and what should be considered low risk, medium risk and high risk.

And it very clearly states what should be done when you're prescribing opioids for these patients. It further elicit what the states, individual states should do when you are prescribing opioids with patients with chronic pain.

Q. Let's pick up with the second bullet. Extensive evidence shows the possible harms of opioids including opioid use disorder, overdose, motor vehicle injury. More risks doctor?

A. That is talking about opioid use disorders, overdose and motor vehicle accidents. These are all risks associated with the utilization of opioids.

Q. And is there any doubt that all of those risks, all of that evidence and all of the controversy that has existed throughout this timeframe, including the 2007 timeframe for which you are opining that Tapentadol, that there was an expectation that Tapentadol could be used to treat

polyneuropathic pain?

A. Yes.

Q. Okay. Now, in 2007, Tapentadol wasn't approved, right?

A. Tapentadol ER was not.

Q. The IR was not approved either, was it?

A. I can't recollect exactly but probably around -- I can't remember the exact date of the approval of the IR.

Q. And so your opinion is again that a person of ordinary skill in the art would use an unapproved drug with all this evidence, with all the controversy, all of the statements we've looked at, for the use of treatment of polyneuropathic pain, correct?

A. I'm saying opioids and opioid like drugs were utilized for neuropathic, polyneuropathic pain.

Q. You yourself, doctor, you remember in deposition you told me that you would use any drug to treat polyneuropathic pain, right?

A. I would not, if I ever did say any drug, I would use drugs that I think would function in the area of polyneuropathic pain. If I said it, I probably meant pain drugs. I mean I would not use a drug for the treatment of, you know, cancer for polyneuropathic pain. I would specifically pick the drugs in the category of analgesics.

Q. You said at deposition when I asked you about

anticonvulsants and I said Would any anticonvulsant, would you use any anticonvulsant for the treatment of polyneuropathic pain? Do you remember what you said?

A. I can't recollect but I can tell you the same answer that I said in the deposition probably is that it is useful for the treatment of polyneuropathic pain. And we had slide demonstration in the Namaka article. I was talking about Gabapentin and pregabalin which are the calcium, they are blockers in the calcium channel.

They are the drugs that he's talking about used for seizure. It is used for seizures, but it is also used for neuropathic pain.

Q. And remember I asked you about Nsaids?

A. Yes.

Q. And you would use any Nsaid for the treatment of polyneuropathic pain too, correct?

A. Nsaids, I would use it as an adjuvant, as a first line drug. Nsaid is like Motrin. And I would prescribe it because it is, if it is severe pain, I would want to give an adjuvant drug so the patients can feel pain relief.

Q. And you would use any antidepressant or tricyclic antidepressants TCAs we talked about?

A. Yes.

Q. And we already heard your opinions on opioids.

What about SSRI? Do you remember we talked about

those?

A. Yes.

Q. You would use those for polyneuropathic pain too, right?

A. Correct.

Q. And SNRA, those too?

A. Some of them are older drugs. So, you know, you obviously try to weigh the risk and benefits. And some other drugs are not as commonly prescribed. But, I have seen patients come to me with all kinds of different drugs being in their universe of practice.

Q. And Gabapentinoids, you would use those, as you just stated?

A. I used Gabapentinoid and pregabalin, both of them for the treatment of neuropathic pain.

Q. And NMDA receptor agonists, you would use that for the treatment of polyneuropathic pain, correct?

A. NMDA drugs are an interesting class of drugs. And, yes, if it is possible to be used, I would utilize them for polyneuropathic pain. But, it generally does not come in an oral formulation. And therefore it is a bit challenging, even though there's some drugs that may have some NMDA activity.

Q. And then I asked you would you use muscle relaxants and neuroleptics. You would use those too for the treatment of polyneuropathic pain, correct?

A. I generally don't use muscle relaxants but --

Q. You told me at your deposition it was not a single pain medication that you would not try for polyneuropathic pain. And then you identified one transdermal patch. Isn't that correct?

A. Transdermal patch in terms of treatment?

Q. Yeah. That was the only one you identified. You would use everything else except for a transdermal patch for treatment.

A. Transdermal patch. Are you still talking about topical agents? If I could get it for polyneuropathic pain if it is possible to utilize, if it is localized to a specific area, I would try a patch, if it's possible.

MR. SITZMAN: Your Honor, do you want to break now? I'm at a breaking point here.

THE COURT: I think so. It's 1 o'clock. So let's break for 45 minutes. We will continue with this.

How much do we think we have on the redirect?

MR. CONNOLLY: I don't think he's done yet, your Honor.

THE COURT: When he's done.

MR. CONNOLLY: As of now I think it's probably ten minutes, your Honor.

THE COURT: Okay.

MR. CONNOLLY: I don't know how much longer he's

got.

THE COURT: I wasn't implying that he had concluded but that's okay.

MR. CAPUANO: I got about a minute or two.

THE COURT: Not a problem. Just trying to get an idea. That sounds fine. Let's meet back in 45 minutes. Let me remind the witness you remain under oath. You are not to talk to your Counsel about the testimony.

Thank you very much. Have a good lunch, everyone.

MR. SITZMAN: Thank you, your Honor.

THE COURT: Thank you.

(Lunch recess)

THE COURT: Everyone have a seat. Let us continue with the cross-examination.

Q. Good afternoon, doctor.

A. Good afternoon.

Q. I just want to continue my cross examination and talk a little bit about the prosecution history in this case.

Isn't it true that all of your invalidity opinions on anticipation and obviousness were made by the examiner and rejected by the examiner who saw and/or oversaw the '130 patent?

A. I believe it is to be true. I believe she looked at it.

Q. But, specifically that she looked at the arguments that

you're now raising were arguments that she identified and that she ultimately rejected when she granted the '130 patent?

A. I cannot tell you what he or she did. But, it is ultimately, it was granted.

Q. Okay. Let's take a look at some of the prosecution history.

Can I have PTX 1600, tab A?

You should have that in front of you.

A. Is that tab one, tab A?

Q. Tab A, exactly. Let's take a look at this. This is the first office action rejection dated April 2, 2009.

Do you see that under the mail date there?

A. Yes.

Q. Okay. Let me have you turn to Page 4 of the office action. And the paragraph that starts with Buschmann there. Do you see that?

It says "Buschmann discloses substances with an analgesic effect, which are suitable of the treatment of severe pain without giving rise to the side effects which are typical of opioids ".

Do you see that?

A. Yes, I do.

Q. And this is, if you can see the top, this is a rejection under 102(b) which is the anticipation section of the patent statute. This is the same argument you're raising,

right, that Buschmann, the '737 patent, the earlier patent disclosed substances with an analgesic effect which are suitable for the treatment of severe pain without giving rise to the side effects.

Isn't that your argument, doctor?

A. Yes.

Q. Okay. Let's turn over to Page 5. And she rejects the claims. She says, Accordingly, the last sentence, no at the top there, "Accordingly, claims 1-4, 9, 14-16 and 18 are anticipated by Buschmann", right? That's your argument?

A. Correct.

Q. Okay. All right. Let's flip over a little bit, Page 7. And the top paragraph and then a little bit into the next.

And then she says that the claims are being rejected under 103, you understand that's the obviousness section, as being unpatentable over Buschmann in view of Dworkin. That was one of the articles that you discussed and that we discussed earlier, right?

A. Correct. We discussed the Dworkin 2003 article. I should say I can't remember this 103 number but --

Q. I will represent to you that that's the obviousness section.

A. Okay.

Q. Okay. And then it says "Buschmann teaches substances

with an analgesic effect" -- the same as we saw before -- "which are suitable of the treatment of severe pain", right?

A. Yes.

Q. And then turn over to Page 8, Rob and the top paragraph, and down. Take it all the way down there to the second paragraph.

And then she says, Buschmann does not teach the use of the compound, where she's giving the chemical formula for Tapentadol, Buschmann does not teach the use of Tapentadol hydrochloride specifically for treating neuropathic pain, especially diabetic neuropathic pain.

Do you see that?

A. Yes.

Q. However, Dworkin, the article we were talking about, Dworkin teaches treatment recommendations of neuropathic pain, right?

A. Yes.

Q. I mean isn't this the argument that you're making here today?

A. I mean, I'm not sure. If you ask me a specific question, I would be more than happy to answer that.

Q. Okay. All right. Dworkin is one of the references that you -- well, here just I wish I had a pointer.

Down at the bottom it says Dworkin details treatment. Isn't that what you said and testified to on direct

examination, that Dworkin and other references, obviously Dworkin details treatment of neuropathic pain with opioid analgesics and treatment of neuropathic pain with Tramadol, right? That was one of the things you said?

A. That's correct.

Q. Where he provides the clinical trial information, adverse effect profile and recommended dosages of the drug.

A. That is true.

Q. Okay. And then the next paragraph down, Rob, the examiner says, In view of the foregoing references, the method of using the instantly elected compound Tapentadol hydrochloride for treatment of neuropathic pain would have been prima facie obvious to one of ordinary skill in the art.

That's exactly your conclusion, right?

A. It said opioids and opioid like drugs can be used for the treatment of neuropathic pain.

Q. Okay. And she came to the conclusion that it was prima facie obvious, right?

A. I read it before several months ago and so I can only tell you what I testified to the fact.

Q. Okay. Well, let's go a little bit farther then in the prosecution history. Let's look at tab E in the history there.

This is the next office action dated February 4, 2010. Do you see that?

A. Yes, I do.

Q. If we turn to Page 5 and we picked up with claims, yeah, that middle paragraph plus a little bit of the -- there you go.

Again, she is rejecting the claims under '130 as being unpatentable over Buschmann, right, '737 in view of Dworkin? Do you see that?

A. Yeah the claims 1-4, 9, 14-16.

Q. Right?

A. Yes.

Q. And she is saying the same thing you are which is that the earlier patent to Buschmann '737, right, the earlier patent discloses, teaches substances with analgesic effects for the treatment of severe pain. And then in response to Mr. Connolly's questions you said, and then there's this law references out there, Dworkin being one of them, that say you can use opioids for the treatment of neuropathic pain?

A. That's correct.

Q. And so your conclusion, just like the examiner, was well this must be obvious then?

A. Yes.

Q. Okay. Turn to Page 6 of the office action there. The little paragraph on the bottom there. Again she says "Buschmann does not teach the use of the compound Tapentadol hydrochloride specifically for treating neuropathic pain, especially diabetic neuropathic pain," right? That was not in

the '737 patent. You agreed with my questions on that?

A. Correct.

Q. Okay. And then the next paragraph down she talks about Dworkin again. However, Dworkin teaches recommendations of neuropathic pain, right?

A. Yes.

Q. Okay. And then let's skip ahead a little bit farther. Let's go to tab G. It's Page 4 of the office action there. Bates stamped 980 in the back. GRTNUC 43980. The bottom two paragraphs, Rob. Thanks.

This is the third time, right, this is now May 2011 and the examiner again is saying the claims are rejected under 103 as being unpatentable over Buschmann in view of Dworkin.

Do you see that?

A. Yes.

Q. So she continues to make your argument for you. Okay. And we turn the page, can we go to the top of Page 6? Take that top paragraph.

Although Buschmann, which is misspelled, although Buschmann does not teach the pain to be treated by his inventive compounds to be polyneuropathic pain, in the absence of evidence to the contrary, treatment of pain taught by Buschmann is inclusive of the neuropathic pain such as polyneuropathic pain and as such a skilled artisan would have been motivated to utilize the inventive compounds of Buschmann

which includes the instantly elected compound in the treatment of polyneuropathic pain.

Do you see that?

A. Yes.

Q. Isn't that the argument you made today in terms of why you believe the patent claims are invalid as being obvious?

A. I believe, I'm not sure, the compounds, but he keeps talking about instantly elected. So I am not sure what that means.

I'm just saying that when you are using it for chronic severe pain, for neuropathic pain, you can utilize opioids and opioid like compounds.

Q. Okay. In fact, in the next paragraph there's something there that's halfway down, middle of the sentence starts towards the end of the right it says Dworkin, et al, details treatment of neuropathic pain with opioid analgesics which include clinical trial, I bet that means data, demonstrating the treatment of diabetic polyneuropathy.

You agree with that, right?

A. Yes.

Q. Okay. And then turn over to Page 7 Rob, top paragraph. In view of the foregoing references, the method of using the instantly elected compound which is Tapentadol for the treatment of polyneuropathic pain would have been prima facie obvious to one of ordinary skill in the art. Right? That's

your opinion?

A. Well, I keep saying that this is, I believe it's talking about the IR version, correct? You are talking about the whole paragraph in the document. I'm not sure. It keeps saying the instantly elected.

Q. Do you recognize the chemical compound as Tapentadol?

A. Yes.

Q. Okay. And it's for the treatment of polyneuropathic pain?

A. Correct.

Q. Now, do you know what the patentee, what Grunenthal did in response to this third rejection in the patent prosecution history? Do you recall?

A. No, it should say -- I forgot. I read all of this well more than a month or two ago.

Q. Okay. Well, let's take a look.

Rob, can you turn to tab I? It's 44045 in the bottom right. It's earlier in the tab.

Do you remember looking at the Christoph declaration that was submitted to the Patent Office?

A. Yes, I do remember reviewing it. But, it's been awhile. But I can skim through it.

Q. Let me draw your attention to just a couple of things. Can you turn to Page 4048 at the bottom right. Actually can you bring up Page 5, right next door, side by side? Thanks.

Do you remember the data and the information that Dr. Christoph submitted to the Patent Office regarding a redesigned Chung model and a redesigned STZ model of polyneuropathic pain?

A. I do vaguely remember talking about it or looking at it.

Q. Did you look at the data in these results?

A. Again to be quite honest I looked at it like really long time ago. I want to say maybe 2, 3 months ago. I haven't looked at it in the recent.

Q. I think you said earlier, I could be wrong, but I thought you said earlier that you were here for the testimony of Dr. Christoph?

A. No. I said I was here for the cross-examination of Dr. Christoph.

Q. All right. Thanks.

When you look at the data here, well, let's look at at polyneuropathic pain .316.

Did you analyze at all the information that Dr. Christoph put forward here and whether or not Tapentadol had delivered unexpected results?

A. Are you talking about Table 2?

Q. Yes.

A. Okay. I believe, again it's without reviewing it recently it's a bit hard for me to go from recollection. But, I believe it's summated to the fact that at .316 dose compared

to the in diabetic SGC model, the .316 dose of Tapentadol was compared to the .316 dose of morphine as the opioid and it was found to be more effective or believed that was the conclusion of the Christoph article.

Q. And we're going to get to the comparison of morphine in just a second. But, I apologize, I don't have a pointer on me.

But, did you look at selective inhibition here of the ability of Tapentadol to treat the diabetic rats while maintaining the nociceptive pathway here in the vehicle, the selective treatment of Tapentadol?

A. I apologize but I don't think I understand your specific question.

Q. Well, I guess the bigger question is, did you consider this data and these results in coming to the conclusion that there were no unexpected results with Tapentadol?

A. I looked at several information, not just this one. So that was my conclusion after looking at all the available literature.

Q. Okay. I'd like you to explain to the Court and me how you can reach that conclusion when Tapentadol demonstrated a three-fold production in the treatment of polyneuropathic pain and the maintenance of the nociceptive pathway as demonstrated in these two models.

A. So, I'm not clear. I'm not sure how you come up with the conclusion of the nociceptive pathway. I see in this rat

model, I believe in this Christoph model, they were all STZ models which it is the diabetic rats. And they gave Tapentadol or vehicle, which is like saline water, and another group of rats with morphine.

So I'm not sure they are piecing out between nociceptive and neuropathic pain. It's my recollection of reading this. Again, I would be more than happy to review them. But, this is my recollection of review of this matter several months ago.

Q. Is it your testimony here today that table one and table two do not show a selective treatment for mononeuropathic and polyneuropathic pain over nociceptive pain?

A. That is generally drugs. Some drugs work at different doses.

Q. I'm sorry, let me just make that clearer.

Is it your testimony here today that Tapentadol does not selectively treat neuropathic pain while preserving the nociceptive pathway as demonstrated in Table 1 and 2?

A. I disagree with your statement.

Q. And did you, you considered, you considered the evidence that you see here, correct?

A. I considered this evidence and this evidence does not point to your question.

Q. Okay . Can you please show me and the Court what it is that you're looking at that does not substantiate the statement

that I made?

A. Because there is no direct comparison between, in the same models with the utilization of in a nociceptive model and a polyneuropathic pain model in this document. I mean the mononeuropathy was looked at and the polyneuropathy, and if you show me -- sorry, I'm not trying to be argumentative. I would be more than happy to look at it.

I just want you to show me. That's all. Because what I look at polyneuropathic pain in this document, I am sorry if I forgot about it, but, I would be more than happy to look at it.

Q. Let's look at table 2. It's polyneuropathic pain?

A. That's correct.

Q. We have a dose here of .316 in the diabetic animal. Do you see that?

A. Yes, I do.

Q. Do you see its significance, the stars, the significance there, it's 15, 30 and 45 minutes?

A. Yes, I do.

Q. Okay. And the same dose .316 in the naive rats. You see there's no significance there?

A. Yes, I mean it doesn't -- yes.

Q. The next one, let's go down to the maximal dose of the one for diabetes and the mean effective dose is 54 and it has significance at every time point.

A. That is true.

Q. And for the very first time at one mg per kg we are seeing an effect finally in the naive rats. Do you see that?

A. Yes.

Q. And those are the first significant results in naive rats, correct?

A. Correct.

Q. Is it your testimony that this data does not show a selective ability to treat diabetic polyneuropathy while keeping the nociceptive pathway intact without any decrease at a .316 level?

A. Yes.

Q. That's your testimony?

A. Yes.

Q. So, you don't see anything unexpected here at all?

A. As I said before, it is useful for the treatment, whether they are demonstrating that it is useful for the treatment of an STZ pain model and it is compared to a vehicle which is, in this case, saline administered compared to the drug Tapentadol.

It does not talk about nociceptive and neuropathic pain pathways.

Q. Doctor, how is this test designed? In order to render that opinion you must know how this test was designed by Dr. Christoph, right?

A. As I said, I would be more than happy to review more. I reviewed this awhile ago. And I can only tell you as we use STZ model in our lab and I can tell you what we do. And without looking at the exact methodology of what he did in his laboratory, I can tell you that we induce diabetes --

Q. Well, I'm not asking about what you did, doctor. I'm asking about what Dr. Christoph did.

Because you're telling us something completely contrary to what Dr. Christoph testified to. And I want to know whether or not you really have knowledge of how Dr. Christoph distinguished this model from the normal STZ model and what he did in order to make this demonstration?

A. I'm not clear on the question but I can tell you that what he demonstrated was that it is useful for the treatment of polyneuropathic pain in the STZ model.

Q. All right. But I want to know do you know how, what his methodology was?

You're here to testify in front of this Court. I want to know do you know the methodology he used to show the significance of treating polyneuropathic pain while maintaining the nociceptive pain pathway.

A. As I can tell you, if you're asking me what he did.

Q. Yes.

A. I cannot tell you what he did because I was not there to see what he did. So I cannot tell you what he did.

Q. You can't tell us what he did either on the STZ side or on the mononeuropathic side, correct?

A. I was not there for either of them.

Q. You can't testify or provide us with any evidence about the subsequent tests that he ran on cite cite synergy, correct?

A. With all due respect, I can tell you that I was not there.

Q. You didn't review any of the evidence that he submitted with regard to the spinal and super spinal tests that he did on polyneuropathic rats, correct?

A. I don't recollect seeing that. But, if you provide it, I would be more than happy to look at it.

Q. You haven't seen and reviewed Dr. Christoph's detailed analysis of all the tests that he ran to make a conclusion that he demonstrated a selective treatment of polyneuropathic pain. Isn't that correct, doctor?

A. I just want to clarify that you specifically asked me before about nociceptive or neuropathic over nociceptive. And what I was saying was in this Table 2 it talks about --

Q. Sorry, doctor, have you reviewed that evidence?

A. Sorry, which evidence?

Q. All of the evidence from Dr. Christoph that demonstrates how Tapentadol works in a polyneuropathic model while maintaining the nociceptive pathway? Have you reviewed that evidence?

A. I cannot recollect if I reviewed all of it. It's impossible for me to know or recollect that.

Q. But, you're offering an opinion that there's no unexpected results here?

A. For clarification purposes, you said look at this Table 2 and tell me if this is selectively inhibiting neuropathic pain or with a nociceptive pathways.

I said looking at that Table 2 I cannot come to that conclusion because this table is only about neuropathic pain.

Q. Except you have absolutely no idea how he set up the model and what he used as the vehicle, correct?

A. You asked me to look at the table. I can only respond to that.

Q. Doctor, correct, you do not know how this test was redesigned and what he used as his vehicle, correct?

A. Correct.

Q. Thank you. Can we have Page 8, please, of the declaration.

This is the third test that Dr. Christoph ran. This is the one you wanted to jump to right away. This is the comparison of morphine and Tapentadol, correct?

A. This is a graph demonstrating the comparison of Tapentadol and morphine.

Q. Right . And do you see where Tapentadol is relative to morphine?

A. Yes, I do.

Q. Is it your testimony that Tapentadol did not outperform morphine in this experiment?

A. In this experiment it demonstrates that Tapentadol is better than morphine at this dose.

Q. So, we're turning now to the prosecution history, doctor.

Can we look at tab H and can we look at Page 5, the paragraph that starts with the present inventors. Bring up the paragraph, the present inventors.

Doctor, Grunenthal told the Patent Office based on the Christoph declaration and the data, that the present inventors have unexpectedly and surprisingly discovered that Tapentadol is extremely and selectively effective for treating polyneuropathic pain and polyneuropathy.

Do you see that?

A. Yes, I do.

Q. I'm sorry.

A. Yes, I do.

Q. I assume, based on your testimony, you think that's a lie?

A. I'm saying that I didn't say that. I said what it demonstrates is that Tapentadol works for polyneuropathic pain in rats.

Q. Do you disagree with that sentence that I just read?

A. I would agree that Tapentadol is effective in the treatment of polyneuropathic pain and that it is generally, again, my understanding from clinical practice that different doses of drugs would need to be utilized for different conditions. So, it is in the fact that Tapentadol does work for polyneuropathic pain.

Q. Okay. Let's look further. Page 6 of the office action at the bottom, one of ordinary skill.

One of ordinary skill in the art reading Buschmann, Buschmann's disclosure that its compounds are useful for the treatment of pain and are effective in the phenylquinone writhing test -- that was the writhing test we looked at in the '593, correct?

A. Correct.

Q. And writhing test would not reasonably expect that Buschmann's compounds would be useful for the treatment of polyneuropathic pain.

Do you see that statement?

A. Yes.

Q. Let's turn over to Page 7, Rob and pick up in contrast in the middle of that big paragraph.

It says In contrast, Tapentadol has a dual mode of action MU opioid receptor agonism and noradrenaline reuptake inhibition. Thus, Tapentadol has a different mode of action than opioids.

Do you see that?

A. Absolutely.

Q. And then the last sentence of that paragraph, Due to these differences in action between opioids and Tapentadol and Tramadol and Tapentadol, one of ordinary skill in the art would not have had a reasonable expectation that Tapentadol could be successfully substituted for the opioids and Tramadol disclosed in what is probably meant to say Dworkin.

You see that, right?

A. Yes.

Q. And turning, actually at the bottom of that page, Furthermore, even assuming the combination of Buschmann and Dworkin rendered the presently claimed methods prima facie obvious, the unexpected and surprising extreme and selective effectiveness of Tapentadol for treating polyneuropathic pain and polyneuropathy effectively rebuts such prima facie obviousness.

The data described in the Christoph declaration demonstrate these unexpected results associated with the presently claimed methods.

Do you see that?

A. Yes, I do.

Q. And you see the description of all those results on Page 8, 9 and 10?

A. I was following you up to that point, but --

Q. Do you see how Grunenthal disclosed what was highlighted in the Christoph declaration at pages 8, 9 and 10 of the office -- of the response to the office action?

A. Yes, I see the results from 8, 9 and 8, 9, yes.

Q. After Grunenthal submitted the Christoph declaration with the data that we just looked at and after it presented this response, what did the Patent Office do?

A. I believe this was in 2011. I don't have that document in front of me.

Q. Well, let's look at tab K. That might help.

Didn't the Patent Office allow the claims of the '130 patent at that time?

A. I believe so.

Q. So, over all of the objections that you identified during your testimony, the patent examiner raised them three separate times. Grunenthal submitted data and the Christoph declaration, some of which you don't remember or don't know about, and that response. And then the Patent Office granted the patent, correct?

A. Yes.

Q. Do you know what Grunenthal did next? Let's take a look at tab L.

A. I'm here.

Q. Do you know what a request for continued examination is

A. Again, I'm not an expert in this field so I'm not going

to comment on that.

Q. You're not an expert in patents, are you?

A. I'm not an expert on the laws surrounding this application process.

Q. You've never participated in the patent prosecution process at all, have you?

A. No, I have not.

Q. And you're not listed as an inventor on any patents?

A. No.

Q. And a request for continued examination is where the applicant, the patentee, sends back to the Patent Office the notice of allowance and asks the Patent Office to look at the claims one more time. And that's what's filed here, I will make that representation to you, the extraordinary step of requesting continued examination.

And do you know what the Patent Office did in response to this?

A. Yes.

Q. Okay. What was that?

A. They granted the application.

Q. It granted the application one more time.

And if we can look at Page 2 of tab M, I will take the bottom and then the top of the neck page, Rob.

At the bottom of the Page 2, the examiner says she has reviewed the submitted IDS and its contents and has determined

that the cited references do not teach nor provide adequate motivation to arrive at the instantly claimed methods.

Do you see that?

A. Yes, I do.

Q. And then at the top of the next page, Page 3, the instant claims are seen to be novel and nonobvious over the teachings of the prior art.

Do you see that?

A. Yes.

Q. As between you and the Patent Office, who has more expertise in evaluating patents?

A. In evaluating patents, I would say the Patent Office.

Q. Now, this last statement that the examiner made that the instant claims are seen to be novel and nonobvious over the teachings of the prior art, you actually agree with that statement, don't you?

A. No. I just said that the treatment of neuropathic pain, polyneuropathic pain with opioids is not new.

Q. So, you disagree with that? You do not believe that the instant claims are seen to be novel and nonobvious, correct?

A. Yes.

Q. Let's take a look at one of your articles.

THE COURT: Let me just ask, any issue with this?

MR. CONNOLLY: No, your Honor.

THE COURT: Thank you.

Q. Doctor, I have just introduced and had marked plaintiff's trial Exhibit 3005 which is an article written by you entitled Multimodal Analgesia for Perioperative Pain Management. Do you see that?

A. This is for the perioperative is acute pain management.

Q. Okay. Let's take a look at Page 61.

Are you there?

A. Yes.

Q. Do you see the dual acting agent Tapentadol? Do you see that?

A. Yes.

Q. Let me read the first sentence that you wrote. "Tapentadol is a novel centrally acting analgesic with dual mode of action".

Do you see that?

A. Yes.

Q. But, you disagreed a minute ago with the examiner who called this novel but yet you wrote in your paper that Tapentadol was novel, correct?

A. That's not what I wrote in the paper.

Q. Correct?

A. Let me finish. What I wrote in the paper was a novel method of treating acute pain. It is a dual method in terms of dual mode of action for opioids and norepinephrine reuptake

inhibition for the treatment of pain.

Q. I'm sorry, doctor, I didn't see the word "acute" there, did you, in that sentence?

A. You are taking the entire topic. If you look at the first page is on multimodal analgesia for perioperative pain management. Perioperative pain management means the first 24 to 48 hours after surgery. It is not talking about chronic pain defined as long months of duration.

Second of all, this is actually an excerpt. This is not a publication. This was an excerpt from a supplement of a review article.

Q. It's funny you say that because you didn't list this on your C.V. as a publication and yet it does seem like a publication to me.

A. It is true. As I said, it is not a publication because this is a review article. This is a lecture among all the lectures I give that you say I am not an acute pain expert, but actually I'm an acute pain expert and a chronic pain expert.

This is one of the international lectures I gave that they decided to print. So, I don't consider that as one of my publications because it didn't go through the peer review process which my publications all, I believe, should go through before it gets published.

Q. All right. Legally let's look at what else you had to say about Tapentadol when you were not having to go through a

peer review process.

You said, the next sentence, combining both effects in a single molecule eliminates the potential for drug drug interactions inherent in multiple drug therapy.

Doctor, Tapentadol eliminates that drug drug interaction, right? Or do you not agree with that sentence?

A. That's correct.

Q. The analgesic effects of Tapentadol are independent of metabolic activation with minimal metabolites, correct?

A. This is true.

Q. And what are you comparing there Tramadol, right? Tramadol has metabolites, correct?

A. Correct.

Q. All right. Let's skip down a few more sentences.

The dual mode of analgesia --

A. I'm sorry, I think I lost you. Okay. I'm sorry.

Q. Sure. The dual mode of analgesia is synergistic as demonstrated by preclinical work.

Do you see that?

A. Yes.

Q. The preclinical work that you're relying on, that's Dr. Christoph's work, isn't it?

A. Probably. I don't see the reference and it is not cited.

Q. Did you do any preclinical work on Tapentadol?

A. No.

Q. Let's go to the top of the next column. This compound though has opioid activity, also has activity at the descending pathway.

Do you see that?

A. Yes.

Q. And is the descending pathway implicated in neuropathic pain?

A. Yes.

Q. Okay. It then says this will be a very useful analgesic as more clinical experience is obtained in the postoperative setting.

Do you see that?

A. Yes. As I said before, this is about acute pain and you are saying that very clearly that it's in the postoperative setting. After surgery it will be beneficial.

Q. Okay. Next sentence, Tapentadol has decreased incidence of nausea and vomiting compared to Oxycodone.

Do you see that?

A. Yes.

Q. That to me reads as in the decrease of side effects. Doesn't that read that same way to you?

A. It decreases in terms of nausea and vomiting. It decreases in side effects.

Q. So, those are side effects that are not as great with

Tapentadol as with Oxycodone, correct?

A. Correct.

Q. Last question, doctor. Can I have DTX 75?

A. Is that in your binder? I'm sorry.

Q. DTX 75.

A. Is that in yours?

Q. Can I have Table 3, Rob? It's column 12. Can you blow that table up, please ?

Doctor, are you there?

A. One second. Sorry.

Q. Okay.

A. Just give me one minute. Yes, I am.

Q. Okay.

A. I'm there at the table.

Q. Have you read this particular example, the in vivo experiments that are here in Table 3 of the patent?

A. Again, I have reviewed this but it has been awhile. So bear with me if I have to read it.

Q. Four compounds were compared, here, right? Morphine, Gabapentin, Tramadol, and what's the last compound?

A. I believe it's compound nine. I believe it's, from my recollection, it's Tapentadol.

Q. So, Tapentadol was compared to Tramadol wasn't it, doctor?

A. I believe so in this animal model.

Q. And Grunenthal provided this information to the Patent Office when it granted the patent, correct?

A. It must have.

Q. Thank you.

MR. SITZMAN: No further questions at this time.

THE COURT: Thank you very much. All right. Are you going to do a further examination?

MR. CONNOLLY: Hopefully very brief, your Honor.

THE COURT: All right.

REDIRECT EXAMINATION BY MR. CONNOLLY:

Q. Dr. Buvanendran, do you happen to have the testimony from your testimony from the Cadence versus Exela trial that you were asked questions about today?

A. Yes, I do.

Q. Okay. I'm going to ask you to turn to page, in the upper right-hand corner it says 1449.

Tell me when you're there, okay?

A. 1449. I'm there.

Q. Okay. And would you turn to the question, do you see there's a question on Page 5?

A. You mean Line 5?

Q. I'm sorry, Line 5. And the answer that goes through Line 12?

A. Yes.

Q. Could you just read that out loud into the record

noting where there's a question and when there's the answer?

A. So, the question was, Can you provide the Court with some details regarding your medical practice?

Response: Yes. My common practice is I do anesthesiology and I practice anesthesiology with routine care of patients with acute postoperative pain and also chronic pain management. In addition I also do clinical development research in the area of active in pain management.

Q. Okay. And can you put up Dr. Haeussler's trial testimony?

Do you recall you were being asked some questions this morning or this afternoon, I kind of lost track of it, about your review of Dr. Haeussler trial testimony?

A. Yes.

Q. You recall that plaintiffs Counsel asked you a series of questions about a certain portion of Dr. Haeussler's testimony?

A. Yes.

Q. Okay. Now, I'm going to ask Ted if you wouldn't mind putting up Page 47, I'm sorry, Page 48, 49. I'll get it right. Yesterday.

So, on Page 49 could you highlight from Line 8 on Page 49 through Line 8 on Page 50?

Now those lines read as follows: "Question: So, there's no question" -- this is inquiry to Dr. Haeussler. "So

there's no question, I would like you to turn to one other page or two pages, the review of Dr. Brodsky. It's about two-thirds of the way through. And we will put it on the screen for you and we will start at Page 4 of 129. And if we could go to the third paragraph Results.

And, again, do you see the reference to the two trials 11 and 15?

"Answer: Yes.

"Question: Okay. Let's turn two pages forward to Page 6 of the 129 summary.

And Dr. Brodsky says in summary, the efficacy of Tapentadol ER in the chronic treatment of pain was from two positive adequate and well-controlled trial studies, 11 and 15. Do you see that answer?

"Yes.

"Question: And then he says, the next sentence, the heterogenous design populations of the two positive trials supports the efficacy of Tapentadol. The two positive trials had different designs, different populations and different types of pain, nociceptive and neuropathic pain. Do you see that?

"Answer: Yes.

"And that's the characterization of the FDA's medical doctor that reviewed these clinical studies, correct?

"Answer: It seems so".

Doctor, is that the testimony that you read of Dr. Haeussler in this trial?

A. Yes.

Q. And what was the significance of that testimony to your opinions stated here today?

A. He talks about the chronic low back pain being more nociceptive.

MR. CONNOLLY: I have no further questions. I believe Actavis' Counsel has some.

THE COURT: That will be fine. Thank you.

RECROSS EXAMINATION BY MR. CAPUANO:

MR. CAPUANO: Can I borrow demonstrative 54? This will be very brief, your Honor.

THE COURT: All right.

Q. Dr. Buvanendran, do you remember Counsel asking you about the legal standard for anticipation and he asked whether the '737 patent explicitly or necessarily disclosed the use of Tapentadol hydrochloride for treating polyneuropathic pain? Do you remember him asking you that?

A. Yes.

Q. Okay. And looking at this demonstrative exhibit number 54, did you think he was asking you whether the subpopulation with severe polyneuropathic pain is necessarily part of the larger population with severe pain?

A. You've got to rephrase. I am not very clear of your

question.

Q. He asked you about the '737 patent and what it was explicitly and necessarily describes. Do you remember that?

A. Yes.

Q. Did you understand he was asking you about what the words were in the patent?

A. He was asking me about the words, yes.

Q. Was he asking you about this Venn diagram?

A. No.

MR. SITZMAN: I object to the form of the question. He is asking the question to, I guess, speculate as to what I was asking or thinking.

THE COURT: I am not sure I understand the question, so you can start again.

MR. CAPUANO: Okay.

Q. When you were asked the question by Counsel about whether the '737 patent explicitly or necessarily disclosed the use of Tapentadol to treat polyneuropathic pain, did you understand that question to be asking you about the words in the patent?

A. Yes.

Q. Okay. In your Venn diagram on slide 54, is the large population, the severe pain, does that necessarily include the smaller population with severe polyneuropathic pain?

A. Yes.

Q. Okay. Let's turn to slide 52.

Do you remember Counsel asking you whether there was any doubt in your mind that example 25 describes Tapentadol?

A. Yes.

Q. And I think you told him you weren't a chemist.

In reaching your opinion that example 25 describes Tapentadol, did you rely on any opinions of other chemistry experts in this case?

A. Yes. I can't recollect their names, but I do rely on them.

MR. CAPUANO: No further questions, your Honor.

THE COURT: Thank you. Anything else? Anything else from the defendants?

MR. CONNOLLY: No, your Honor.

THE COURT: Anything else from the plaintiffs?

MR. SITZMAN: Nothing, your Honor.

THE COURT: All right. Thank you very much. Your testimony is concluded today. The Court thanks you for coming in and assisting. I do appreciate it. You may go. Thank you.

THE WITNESS: Thank you.

THE COURT: Where does that leave us, Counsel?

MR. SITZMAN: I think it's the defendants' move to rest at this point.

MR. CONNOLLY: We so rest.

MR. ALY: Before we rest, we want to make sure the Exhibits -- two things, just for the record purposes. I will use the microphone.

THE COURT: Speak right into it. See if you can pull it a little closer.

MR. ALY: One thing is the exhibits. As your Honor knows, we have been exchanging lists of exhibits. So, when we close, it will be subject to the exhibits being made part of the record officially, which they haven't been done. And the second thing --

THE COURT: Did you agree upon another list? The initial list that you gave us, we put on the record. Is there a second list now?

MR. SITZMAN: There will be a second and a third. There is not an issue. We are kind of lagging behind making sure we get through the transcripts, making sure we have all the exhibits.

THE COURT: I completely understand.

MR. SITZMAN: And there's no objection to Mr. Aly's preservation.

THE COURT: Excellent.

MR. ALY: The two points. The second point, your Honor, has to do with deposition transcripts which the Court order procedure is to just submit those separately. So, when we close, they will also be subject to those deposition

transcripts which will be of record. Of course the two in mind are Marita Mueller and Dr. Tzchentke that were relevant and referred to in the case.

THE COURT: Any issue?

MR. SITZMAN: No objection here, your Honor. In fact, I think we are going to start discussing how those should be submitted to the Court.

THE COURT: That's fair enough.

MR. FITZPATRICK: I will just note for the record, your Honor, that Mr. Aly is speaking on behalf of all defendants on these issues.

THE COURT: That sounds fine. Thank you.

MR. ALY: Those are the only two.

THE COURT: So, the two issues I think we have dealt with is the first one is the exhibit list. It sounds like you're still going through it, catching up with the record and you're going to be submitting something formal. I will treat it in the same way that I dealt with the first exhibit list. So, once you're in agreement, you can let me know and then I will put it onto the docket.

And the second issue with respect to the depositions, you're still talking to one another with respect to how you're going to be, I guess the process for submitting them. Or what is it exactly that you're still discussing?

MR. SITZMAN: I was going to make a proposal that

we handle the plaintiff witnesses, the color coding for the designations, their designations and ours, have the defendants handle all their witnesses, then we can hand them over and then hand them to you.

THE COURT: How does that sound?

MR. ALY: That sounds fine.

THE COURT: Mr. Aly is speaking for all the defendants?

MR.FITZPATRICK: Yes, your Honor.

MR. CONNOLLY: Yes, your Honor.

THE COURT: Are we good with that? Yes. Thank you. That sounds fine. That seems pretty straightforward.

MR. SITZMAN: I guess on that topic, your Honor, as long as we get them to you in the next few days, is that all right, by Thursday maybe?

THE COURT: That's fine. I know you folks have your hands full.

MR. SITZMAN: Thanks.

THE COURT: Where do we stand now?

MR. ALY: I think we do rest at that point.

THE COURT: All right.

MR. SITZMAN: Your Honor, I just want to preserve and sort of make the 52(c) motion as to Roxane and Alkem on the infringement issue.

The Court's already heard argument on that. I

don't think there's any need to do that. The Court's already indicated that it will reserve. But, I just wanted to formally make sure, now that they've closed, to request that.

THE COURT: That makes sense to reserve your rights with respect to that. But, as I indicated with the other application, I will be reserving on this as well because it is a complex matter and I would like time to reflect on the issues.

So, at this point I will be reserving on that as well. Thank you.

MR. SITZMAN: One more thing.

THE COURT: Yes. Go ahead.

MR. SITZMAN: I just need to get clarity on something.

THE COURT: One more thing with respect to that in terms of doing our closings. I know we have set aside a separate date for doing our closings. I am anticipating also doing essentially what is a motion argument at that point in time as well.

So, we can talk about it as we get closer to the date. But, I'm sure you folks want to put together your own presentation. But I want, I do want to allow time for my own questions and an argument regarding the issues that we've had here.

MR.FITZPATRICK: Of course.

THE COURT: As opposed to a sterile argument which I appreciate and certainly I'm looking forward to hearing. But, I also have some issues that I would like to get further development of. And I think it would be productive if we all discuss it together.

MR. FITZPATRICK: Certainly.

THE COURT: Thank you.

MR. SITZMAN: We will talk hopefully later this week about timing and schedules and things like that.

THE COURT: That sounds good. Do we think we are going to be done this week or not?

MR. SITZMAN: I haven't heard about the rebuttal case but we're hoping to be done by Thursday.

MR.FITZPATRICK: I think that's the defendants' consensus also, your Honor.

MR. SCHULER: Based on our understanding of how much time is left.

THE COURT: How much time is left on either side?

MR. SCHULER: My understanding is we are up to 25 hours before today, which is --

MR. CONNOLLY: And seven hours after that, today, your Honor.

THE COURT: Is that it? No, I'm joking.

MR. SCHULER: It depends on how you accelerate time. So, our understanding, based on we have been getting six

hours a day, we may ask the Court if we can go late. I don't know which day we need to do it. I hate to do it Thursday. But even a little bit, half hour here or there, I think we will finish.

MR. SCHULER: Or run out of time.

MR. SITZMAN: As long as they stay within their allotted time, I'm sure that's going to work out fine.

THE COURT: And obviously if you don't complete what you need to do by Thursday, I would anticipate that you'd have whatever witnesses you actually need for the following Monday. Would we be prepared to do that? I'm pushing to do, I think it would be great if we finish on Thursday.

MR. SCHULER: Based upon who they already proposed for Wednesday, that is their final two rebuttal witnesses, and then there are simply two secondary additional witnesses that are fairly short.

THE COURT: I'm sorry, again, the numbers count between the hourly count for the defendants and the hourly count for the plaintiffs is what, roughly?

MR. SCHULER: Aggregate 25.

MR. FITZPATRICK: I think we would have to redo the count at the end of the day.

THE COURT: It's 25 plus seven on your side?

MR. SCHULER: No, combined the two sides have about 25.

MR. SITZMAN: I've got 25 hours for the defendants and 19 hours for us.

MR. MILLER: As of last night, or last week.

MR. CAPUANO: Our numbers are close to that.

THE COURT: Okay. So, not counting today.

MR. SITZMAN: Not counting today.

MR.FITZPATRICK: So, that would leave about 26 before today.

THE COURT: All right. So, we'll see how it goes.

MR. SITZMAN: Your Honor, with the defendants resting, we sure would like to get our next witness on quickly. Is that okay? Don't take a break yet and go ahead and move on.

THE COURT: Are you good? Would you like to just start? All right. Five minutes, the short, short break. Short, short break.

MR.FITZPATRICK: Thank you, your Honor.

(Whereupon a short recess was taken.)

THE COURT: Let's call the next witness, please.

MS. RANNEY: Plaintiffs would call Dr. Joel Bernstein. But, I believe we have binders to hand out first.

THE COURT: Good afternoon. Let us have the witness sworn in.

J O E L B E R N S T E I N, sworn and testifies as follows:

THE COURT: How are we doing on the exhibit binders? Did we get an opportunity to take a look?

MR. ALY: Yes, your Honor. No objection to the exhibits. As to demonstratives, there's new material not in Dr. Bernstein's report, particularly with slide ten. However, given that this is a bench trial, what we'd suggest is that we just cross-examine on that slide which has to do with the timing of various techniques.

THE COURT: That sounds fine. I'm sure there's no problem with that.

MS. RANNEY: That's fine. And, your Honor, we believe that these slides are also supported in Dr. Bernstein's report and we are happy to go through that.

THE COURT: Thank you. All right.

DIRECT EXAMINATION BY MS. RANNEY:

THE WITNESS: I didn't state my name yet.

THE COURT: You can state it.

A. My name is Joel Bernstein.

Q. I'm Christine Ranney of Gibson Dunn for Depomed.

THE COURT: Thank you.

Q. Good afternoon, Dr. Bernstein.

A. Good afternoon.

Q. Let's put up plaintiff's Exhibit 1034.

What's this exhibit, Dr. Bernstein?

A. That's my C.V.

Q. And is this C.V. accurate as of the date in the top right corner?

A. Yes, the upper right-hand corner of this is July of last year. It's accurate as of that.

Q. Any material changes since then?

A. There may have been a few additional publications or talks that I've given, papers we've submitted. But that's essentially it.

Q. I'd like to walk you through your employment and educational background.

Did you help prepare any slides to aid your testimony today?

A. Yeah. We have a demonstrative I think that summarizes some of that.

Q. All right. Let's put up the first slide.

Could you tell the Court about your educational background, Dr. Bernstein?

A. Yes. Actually there should be another line below where I went to school. I'm sort of on a homecoming trip here. I went to high school up the hill here in West Orange, New Jersey. So I'm a little bit of a local boy.

And then I went to, I was an undergraduate at Cornell where I did a Bachelors degree in chemistry. And following that I did my Masters and Ph.D. at Yale in physical chemistry and mainly on spectroscopy. And the title of my thesis is

given there.

Q. What is your current professional affiliation?

A. My current affiliation is I'm global distinguished Professor of Chemistry at NYU. And I split my time between one semester at NYU in Abu Dhabi and another semester in Shanghai. I'm currently actually in Shanghai.

Q. How long have you been a faculty member?

A. I took my first faculty job in October of 1971 so it's been about 45 years.

Q. Let's go to the next slide.

What does this slide show?

A. This slide summarizes a number of the positions I have held over the years. Most of my career, my academic career was at Ben-Gurion University of the Negev in Israel. And that was punctuated by visiting Professorships and sabbaticals at a number of other institutions which are shown here.

Q. And in the 45 years that you've been a faculty member, has there been a common thread throughout your research?

A. Yes. Most of my work has been on the solid state chemistry of molecular crystals e have been interested in the structure and properties of molecular crystals with a particular emphasis and my greater interest in polymorphism.

Q. And how did you first become interested in polymorphism?

A. Well, back in 1965 or '66 when I was in the late stages

doing my Ph.D., I was working with another graduate student on trying to work out some of the geometry of a particular crystal. And we were having a difficult time.

So, he said, you know, maybe this is, this material is polymorphic. And I said what's that. He said well, it could have more than one crystal structure. And I was fascinated by the idea that a particular substance could crystallize or a particular molecule would crystallize in more than one crystal structure.

And that was sort of a milestone in my entire career and I've been interested and fascinated by this ever since.

Q. Are you still active in research on polymorphism?

A. Yes, I am.

Q. Let's put back the C.V. and go to Page 5. Memberships and professional societies.

Now, one of the items listed here is Fellow, American Association for the Advancement of Sciences.

What's that one, doctor?

A. Yeah, the American Association for the Advancement of Science of course is an important professional organization which publishes the Journal of Science. And every year they elect a few hundred Fellows for special recognition on accomplishments, career accomplishments. And among those are a few foreign Fellows.

And since I was in Israel when I was elected a Fellow,

that was as a foreign Fellow back in 1999.

Q. Is this a fellowship you still hold today?

A. Yep.

Q. Let's go to Page 6, the next page. The scientific publication section.

Does this section reflect your publications related to polymorphism?

A. Yes, it does. Most of the publishings in there deal with polymorphism.

Q. And how many books or chapters have you written on polymorphism?

A. Well, the first entry there is a book I wrote which came out what, about 14 years ago, and was translated into Russian in 2008. And then there are 17 or 18 chapters and another 170 or 80 papers. So, the total list of publications is approaching about 200.

Q. Okay. And is this the book you are referring --

MS. RANNEY: May I approach?

THE COURT: Yes?

Q. -- the book you are referring to?

A. Yes, it is.

MS. RANNEY: I am going to hand this to the witness. For the record, this is plaintiff's Exhibit 1041.

Q. How did this book come about, Dr. Bernstein?

A. Well, about in the early '90s when I had been working

in this field for quite a few years, I realized that there was, there had been a lot of activity. And polymorphism was actually discovered about 1821. And many more people were starting to work in the field. But, there was no, there was no texts in the field.

And I decided to write this book in order to accomplish really two purposes, one was to set out the fundamentals of polymorphism and molecular crystals. And so the first four or five chapters do that. And then summarize a lot of the work that had been done until then.

So that the book could serve as a starting point for people who want to get into the field, and then serve as a point for further work as more and more work was published.

Q. And do you know roughly how many times your book has been cited?

A. Yes. It's been cited, I think, a little bit over 1400 times already.

Q. And have defendants' experts relied on your book before in their books?

A. Yeah, I think Dr. Metzger cited it 12 times and Dr. Steed 9 times, last time I checked.

Q. Let's go to Page 9 at the top. What's listed on this page?

A. These are, this is the beginning of the list of peer reviewed publications and scientific journals.

Q. You mentioned earlier that your total publications were approaching the number 200.

Do you know about how many times your publications have been cited?

A. I think somewhere over 16,000.

Q. I would also like to ask you about one of the articles listed on your C.V., if we could go to plaintiff's Exhibit 680.

What's this article?

A. Well the article's entitled Polymorphism, a perspective. And it was published in Crystal Growth and Design which is an American Chemical Society Journal. It was founded in 2001.

Now, as the journal approached its tenth anniversary, the editor decided to invite key people in the field to write what they call perspective articles, sort of reviews on the main topics in the field. And I was invited to write that one on polymorphism. And so that's how this particular paper was generated.

Q. How does the scientific content of this article compare to that of your textbook?

A. Well, since I had published my book in 2002 and this was going to be published in 2011, what I decided to do was try to cover some of the progress that had been made in that decade and as well as layout a number of the remaining problems and challenges that we're still faced in research on polymorphism.

Q. Now, did you help prepare a slide summarizing the expertise that you've just described that's relevant to the subject matter you will be discussing today?

A. Yes, there is a slide of that nature.

THE COURT: You know what, before we get to the slides, Mr. Aly, I didn't get from you which is the slide that you have an issue, I know you are going to talk about it on cross-examination. But just so I understand, which slide was it?

MR. ALY: Number 10.

THE COURT: Number 10. And the response to that is the subject of it was in fact contained in the expert report?

MS. RANNEY: That's correct.

THE COURT: Okay. Briefly what is the slide on?

MR. ALY: On timing of various things. So there's a difference between, in the report, discussions of finding polymorphs versus the time it takes to do different tests and techniques for the polymorph discovery process.

THE COURT: Okay. I know you mentioned timing but that's a little more specific.

MR. ALY: That's what I meant.

THE COURT: And the response was that -- was this fact part of the expert report?

MS. RANNEY: Yes. Dr. Bernstein discusses how,

you know, experiments can take different amount of time, sometimes many months. And he discusses some of the techniques on the slide in his report.

THE COURT: Okay. Thank you.

A. Yes, this is a summary of my research interests throughout most of my career and today as well.

MS. RANNEY: Your Honor, plaintiffs offer Dr. Joel Bernstein as an expert in the field of solid state chemistry and polymorphism.

THE COURT: Any issue with that?

MR. ALY: No, your Honor.

THE COURT: Thank you. He is so deemed an expert in those areas.

MS. RANNEY: Thank you.

THE WITNESS: Thank you.

Q. Doctor, were you asked by plaintiffs to provide any expert opinions in this case with respect to U.S. patent Number 7994364?

A. Yes, I was.

Q. What opinions were you asked to provide?

A. I think my opinions are summarized on the next demonstrative. I was asked to opine on validity of the '364 patent, including utility, obviousness and anticipation with respect to that patent. And the issue of enforceability which involved defendants' claim of unclean hands on the part of

Grunenthal.

Q. And did you reach any conclusions with respect to the validity and enforceability of the '364 patents?

A. Yes, I did.

Q. What were those conclusions?

A. I think the patent demonstrates utility, it's nonobvious and the material in the patent was not anticipated.

Q. And did you reach conclusions on enforceability and and --

A. And Grunenthal did not demonstrate unclean hands in applying for the patent.

Q. Okay. Let's put up plaintiff's Exhibit 1458.

If you can sort of highlight the top.

Do you recognize this document, doctor?

A. Yes, that's the '364 patent.

Q. And if we go back to the whole patent, what is the invention of this patent?

A. The invention I think is pretty well summarized both in the title and the abstract. So if we could see the title. No, the title. The abstract does it as well.

Q. The title is fine.

A. The title says this is crystalline form so the patent deals with crystalline forms of Tapentadol. And the abstract again, a hitherto unknown crystalline form.

So the patent deals with that and how to make it. And

then the patent also describes the use of that as an analgesic to treat pain and/or urinary incontinence.

Q. Is the invention of the '364 patent useful?

A. Yes, it's useful essentially for two reasons, one, it provides the method of preparation and the characteristics for form A which is a stable form, stable crystalline form of the material at room temperature. And it also describes its use as an analgesic.

Q. And does the '364 patent provide data showing that this form A is the stable crystalline form at room temperature?

A. Yes, it does. And I think that's, if we go towards the end of that specification, just before the claim, I believe it's example 16, if I remember, if I recall correctly.

Q. Yes, that would be Bates 57606, PDF Page 18.

So what does example 16 show us, doctor?

A. Example 16 is titled Variable Temperature X-ray Powder Diffraction Experiment. And then as is written, a variable temperature x-ray powder diffraction experiment was run thereby producing form B from form A. Form A converted to form B from 40 to 50 degrees during the experiment. The result is reversible with form B changing over into form A at lower temperature.

So, that means that the experiment was begun at room temperature and the material was heated up. And in the course of heating the material up, it was monitored using x-ray powder

diffraction and a transition or phase change, as we say, from form A to form B occurred at the higher temperatures, namely from 40 to 50 degrees.

The last sentence in that paragraph says, The result is reversible with form B changing over into form A, indicates that form A is the stable form at room temperature.

Q. Thank you. Let's move on to a different topic.

Were you in court for Dr. Steed's testimony regarding obviousness?

A. Yes, I was.

Q. And do you agree with Dr. Steed that the claims of the '364 patent are obvious?

A. Not at all.

Q. Could you give us one reason you disagree?

A. Well, no crystal form is predictable. And predictability is essentially, from a scientific point of view, a synonym of obviousness. Nobody could look at the '737 patent and have any idea what crystal forms would be possible from Tapentadol.

Q. Do you address the predictability of crystal forms in your book?

A. Yes, I do. And that's on --

Q. If we could go to plaintiff's Exhibit 681.

A. That would be on Page 241.

Q. All right.

A. Which is the chapter on polymorphism and pharmaceuticals. And in the middle of the first paragraph on Page 241 where it says while, that's the part, and I'll read that.

While it may not be surprising that many pharmaceutically important materials have been found to be polymorphic or that any particular compound may turn out to be polymorphic, every compound is essentially a new situation. And the state of our knowledge and understanding of the phenomenon of polymorphism is still such that we cannot predict, with any degree of confidence, if a compound will be polymorphic, prescribe how to make possible unknown polymorphs, or predict what their properties might be.

And that, of course, was written in 2002.

Q. And what do you mean when you say "every compound is essentially a new situation"?

A. Well, there are a lot. Scientists naturally would like to be able to predict when polymorphs might appear. So people have done a lot of statistics and say there are certain factors which might influence the presence or the formation of polymorphs. And even with those statistics, which we will talk about in a few more minutes, when you have a specific compound, nothing is known about it and nothing can be predicted.

And so the meaning of every compound is essentially a new situation. When we started with a new compound, we have no

idea what the possibilities are. And so that involves a considerable amount of research.

Q. And you wrote this opinion quite awhile ago. Is it still true today?

A. Pardon me.

Q. Sorry. Is this still true today what you wrote?

A. Absolutely. It hasn't changed at all.

Q. Do others in the field agree with you?

A. Yes, they do.

Q. Let's put up plaintiff's Exhibit 691. Call out the title and authors.

Are you familiar with this article, doctor?

A. Yes, I am.

Q. Does this article address whether polymorphism was predictable in 2004?

A. It does.

Q. What's the general thrust of what it says?

A. The general thrust is it was not predictable. And we can go on and read I think the relevant passage.

Q. Sure. Let's go to PDF Page 22, Page 296 of the article.

I direct your attention to the first full paragraph on the right column. And there's a sentence in the middle of the paragraph beginning Unlike salts. The first paragraph on the right beginning For many years. And the sentence beginning

Unlike salts.

A. In the middle.

Q. There we go. If you can just read this sentence for the record.

A. Unlike salts, which for the most part can be prophetically claimed based on an understanding of the chemical structure of the compound and its ionization constants, the existence and identity of hydrates, solvates, co-crystals and polymorphs have defied prediction.

Therefore, in order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials.

Q. All right. And do you agree that the identity of hydrates, solvates, co-crystals and polymorphs have defied prediction?

A. Yes. That's just affirming what I said earlier.

Q. Is it possible to predict whether a compound will be polymorphic based on molecular structure?

A. Not at all.

Q. Have you investigated the inability to predict polymorphism in your own work?

A. Yes. And we're still doing that. In fact, very

recently last summer we published a paper which addressed that specific question.

Q. Could you tell us a little bit about what you found?

A. The paper's actually called Facts and Fictions about polymorphism. It was published in Chemical Society Reviews which is the review journal of the Royal Society of Chemistry in London.

And we were curious about really whether there could be any molecular predictor. If you can look at a molecule and find any feature in the molecule which could be a predictor of polymorphism.

And so we based our research on the data what's called the Cambridge crystal graphic, the Cambridge structural database which is a depository for all the crystal structures that have been done in Cambridge at the University of Cambridge. And there are probably about 800,000 over there now. And this has been going on since 1965.

And I actually had two colleagues who worked with me, both of them, one is from Eli Lily and the other is from Roche. And we investigated what possible factors could be important on a molecular basis. If you look at a molecule, it's got certain features to be a predictor of polymorphism. And we found that there is no, no molecular feature which can be used as a predictor of polymorphism.

Q. Did you hear Dr. Steed testify that about 50 percent of

compounds exhibit polymorphism?

A. I heard him say that.

Q. Do you agree with him?

A. Well, the statistics, I don't agree with that. I mean I do, well, in a way I do agree. And I should probably explain it.

The statistics on polymorphism are very difficult to obtain. So, for instance at one extreme if you look in the Mercks index which contains about 10,000 compounds of pharmaceutical importance, and look up how many of those are polymorphic, it's about one or one and a half percent. So that you might say that's the low end and that obviously is contrary, completely, to what Dr. Steed said.

On the other hand, it was a study by Pat Staley who was a scientist who worked at SSCI, you've heard about SSCI, for a number of years. And SSCI's business, they were in the business of contracting, they were asked by pharmaceutical companies under contract to search for polymorphs. So, that was how they were making their money. And Pat Staley summarized many years of their work, looked at about 250 compounds or so.

So, here was a concerted effort to look for and find polymorphs. And in that instance they found about 48 percent of the compounds that they looked at exhibited polymorphism. So, that would be, that would be the high end. Our numbers

that we found last, we published last summer, are considerably lower.

Q. Could you tell us about those numbers or a little bit about them?

A. Those numbers are somewhere in the range of about 30 to 35 percent.

Q. Have others in your field written about the inability to predict polymorphism based on molecular structure?

A. Yes, they have.

Q. Could we go to plaintiff's Exhibit 684? Let me just go back to the title of the article which is Crystal Gazing: Structure Prediction and Polymorphism.

A. Yeah, this is a paper in science from 1997, as I recall, from the author Gautam Desiraju. And Gautam Desiraju is a colleague, you can call him a friend, who established a very active group in India for many years in Hyderabad. He recently moved to the Indian Institute of Technology in Bangalore. And he was, until recently, president of the International Union of Crystallography which is a worldwide organization of crystallographers.

So, he is a real authority in the field. And he wrote this paper commenting on the prediction, our ability to predict polymorphism back in '97. And if you can go to the appropriate section.

Q. Let's call out the bottom of the middle columns or

about five lines down.

Could you read this last sentence beginning All this means?

A. Sure. "All this means that the crystal structures of many 'simple' organic compounds need not be simple at all. What is surprising, however, and this is what provides the vital impetus to molecular chemistry.

Q. Sorry. That's not quite right.

A. No, that's not it.

Q. Go to sort of the paragraph begins --

A. It goes down to the subject. It's under the caption on the right-hand side. "Vital impetus to the subject, is that although the energy differences between the plethora of putative crystal structures for a given molecule can be quite small, many organic compounds are not polymorphic.

Molecules seem to know exactly how to crystallize, even as chemists seem unable to accurately foresee such events".

So, this just again shows how little we know about the possibility of polymorphism and the lack of our ability to predict it.

Q. And would this have been the case in 2004 as well?

A. Absolutely. It's still the case. It hasn't changed at all.

Q. Okay. Let's go to plaintiff's Exhibit 693. If you can call out the title and authors.

A. Yeah.

Q. What's this about?

A. You don't have the reference up there. If you get the, stop, the reference is actually from chemical reviews. So which I point out is the most highly, it's the chemistry journal with the highest impact factor. So, this was from 2001.

The second author, the Professor Zaworotko also had a distinguished career here in Canada and Florida. And he has now been put in charge of the pharmaceutical research unit at the University of Limerick which is part of a consortium of seven Irish universities developing pharmaceutical research and development techniques.

Q. If we can go to the second page, that's Bates Number 64169, and call out the two sentences are From molecules to Crystal Engineering, could you read the first two sentences into the record there?

A. Sure. You will note, this is a quotation and so they are quoting "One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition".

And then Mike Zaworotko notes this provocative comment by Maddox illuminates an issue that continues to represent a challenge of the highest level of scientific and technological

importance.

Just to note that Maddox was, at the time, the editor of nature this is a quotation which perhaps has haunted people in our field because we haven't made a whole lot of progress since then and been able to do that.

Q. Let's talk more specifically about Tapentadol hydrochloride.

Would a person of ordinary skill in 2004 be able to look at the molecular structural of Tapentadol and predict whether it would be polymorphic?

A. As I pointed out, they couldn't do it then and they can't to it now. So there's no way that could have been done.

Q. And how many forms of Tapentadol do we know about today?

A. We know about two crystalline forms and there's an amorphous form.

Q. And is it possible that there would be other crystalline forms?

A. Absolutely. We just, there may be, but we haven't discovered them yet.

Q. Is it possible that these other forms may be more stable than form A?

A. If we, if other forms appeared, it would be likely that they would be more stable. The person who first really looked at this whole situation of stability was sort of the father of

physical chemistry, a man named Oswald, a great German physical chemist in the 1890s. And he pointed out that if a material is polymorphic, then as more, as new forms appears, the later appearing ones will be in general more stable than the ones that appeared before that.

This is called Oswald's rule, not Oswald's law. So there are exceptions. Like every rule there are exceptions. There are exceptions to that as well. So that's on the basis of Oswald's observation. That's what we would expect if and when we find any new forms.

Q. Could you provide the Court with a well-known example of a more stable crystal form appearing late in the game?

A. Sure. One of the first that I encountered was ranitidine hydrochloride which is the active ingredient in Zantac. And the hydrochloride, ranitidine hydrochloride was first prepared in 1977. And then Allen & Hanburys which was the predecessor of Glaxo at the time where the material was being studied, worked for four years on that compound before anything new was discovered.

And then one day one batch in a pilot plant appeared in a new form, and that was the second polymorph. And in fact that was the polymorph that then Glaxo started marketing as Zantac in 1984. So, that was a serendipitously beneficial incident.

But later, later on back in 1998 Abbott Laboratories

was marketing a drug called ritonavir and which was used, it's an antiviral compound which was part of the AIDS cocktail.

And in 1998, two years after they had launched and that was on the market, they had made 240 batches. And there were something on the order of 50,000 AIDS patients taking this material. And I think the market was somewhere in the order of $200 million. A new form appeared. And in concert with Oswald's rule, that new form was more stable. And the more stable forms are less soluble. And so that new form had essentially no therapeutic value.

And Abbott, which was at the time I remember the fifth or sixth largest drug company in the world, couldn't find a solution to go, they wanted to go back to the earlier form, and they couldn't really figure out how to do it. And the drug went off the market for a year while they searched.

And there was the story of their search is a fantastic story. But, they finally, after a year, didn't solve the problem by being able to go back to the original form. But, they developed a gel capsule. A gel capsule is essentially a solution in a pill. So that's, and that's how they solved the problem.

So, new forms can come along at anytime. Sometimes the pharmaceutical companies continue to look for them. And sometimes they come along, whether they are desired or not. And there's the two cases I gave, one where it was a good thing

and the other one where it was at least a public relations disaster.

Q. So, with Ritonavir, you said they launched the drug and they had 200 batches and they only then dissolve the more stable form?

A. They had no idea if that form could exist. And, as I said, they were on the market, 240 plant batches that they had made before this appeared. And it took them a few years to figure out how that happened.

Q. Let's go to plaintiff's Exhibit 668 and call out the heading title.

Are you familiar with this document, Dr. Bernstein?

A. Yes. That's the '737 patent we've heard a lot about.

Q. And did you hear Dr. Steed testify that the '364 patent is obvious in view of the '737 patent and other references?

A. Yes, I heard him say that.

Q. Do you agree with him?

A. Not at all.

Q. Does the '737 patent include Tapentadol hydrochloride?

A. Yes, it's one of the many compounds that are mentioned in the patent.

Q. And what other compounds does the '737 patent include?

A. Well, there's a huge number which I actually haven't calculated. I think somebody has. But, I am not familiar with it. But, there are, I think, 28, if I recall correctly, named

compounds which are included there.

Q. Does the '737 patent disclose specific crystalline forms of any of these compounds?

A. No, the whole concept of crystalline forms is not mentioned in that patent.

Q. So, it doesn't disclose any of the compounds as polymorphic?

A. No. The word "polymorph" doesn't appear in the patent.

Q. Did you hear Dr. Steed testify that the '364 patent is obvious in light of the '737 patent and references discussing polymorph screens?

A. Yes, I did.

Q. And what is a polymorph screen?

A. Well, a polymorph screen probably should be more properly called a crystal form screen. And the idea is that when a pharmaceutical company has an active compound -- I should mention it's not only pharmaceutical companies, industries that work in pigments and in explosives and anything that deals with solids, they would like to know what is a whole variety of solids that might be possible for a particular material. So, that would be a crystal form screen.

And what it means is doing, trying to set up a whole set of almost an infinite variety of experiments in order to discover and characterize all the crystal forms that are possible for the particular compound of interest and then

choose the one or ones, in some cases, that might be best suitable for the purposes that the company is interested in.

Q. Have you prepared any slides to help demonstrate what one might be looking for in a crystal form screen?

A. Yes, I have.

Q. If we can go to slide 7.

A. This is sort of a brief tutorial to demonstrate what we are talking about with polymorph and the screen.

So, I apologize if it's a little bit too simple because the idea is in solution, which we have all these molecules which are representatives as human stick figures, and in solution the molecules tumble around in a random way. And what we want is a solid. And solids are characterized, crystals are characterized by a regular order.

So, when these molecules come together to form a crystal, then we can get a crystal structure which is up in the upper right-hand corner. And you can see all the molecules there are well organized in a regular fashion. Of course this is a two-dimensional demonstration. It could be crystals that are three dimensional.

And the whole idea is that well, as I said when I was fascinated in 1965 about polymorphs, it doesn't have to be just that way. The molecules can arrange themselves in another way. Let's see like that. See then these would be two different molecules and you can easily see that the same molecules are

arranged in different ways.

And then the idea is if they are different structures, since the properties depend on the structure, then different polymorphs can have different properties.

The example that we often use is diamond and graphite which are both crystal structures of carbon, although not strictly polymorphs in this sense because the bonding is a little bit different. But, they are both carbon and of course they have very different properties. So, this is a polymorph. And as I said, this isn't the only limitation.

Q. For the record, we have moved to slide 8.

A. Again, I'm showing the molecules here. I should point out I am showing the molecules up on the left and these are in a solution and so which the molecules crystallize. You see on the right there's the regular order that we saw before. But, the molecules of the solvent can be incorporated in a regular fashion.

If it's water, it's called a hydrate. And if it's a solvent, then we call it a solvate. So, the crystal form landscape as we say can have polymorphs, they can have polymorphs, solvates, hydrates and polymorphs of solvates and hydrates. And you will see in a minute what we mean by that.

Q. It looks like this is actually slide 7. So let's go to slide 8 now.

A. Okay. So this demonstrates the variety of

possibilities when you start out with a particular compound and what can happen.

So, let's say if a pharmaceutical company is investigating a molecule decides to pursue the development of that molecule, then what we have is a free molecule. We have identified a molecule which is active. And we want it as a solid. And that can be polymorphic which is what I showed two slides back.

But then you can have a salt and we're talking here again this Tapentadol is a salt because it's Tapentadol hydrochloride. So that can be polymorphic. But, that's not all. Because, as you saw, we could have the hydrates of the salt and that can be polymorphic.

And we can have a solvate which is in which the solvent is included. It's not water, but some other solid. So it could be a methanol, ethanol or something like that, and that can be polymorphic.

So that's what we are talking about with the salts. But, again, the free molecules can also have a hydrate and that can be polymorphic. And if the included solvent is not water but some other solvent, that's a free molecule. So these are many, essentially all the possibilities when you start out with a compound that you're looking at exploring the crystal form landscape, in answer to the question what are you looking for.

Q. If a crystal form screen was to be conducted on a

particular compound in 2004, does the prior art point a person of ordinary skill in any particular narrow direction?

A. It doesn't say anything about how to begin or what to do.

Q. Could you expand on that a little why it doesn't say anything about what to do?

A. You see you have here either the salt or the free molecule. And you start out and you have a solid. And now you'd like to start investigating this landscape. So you have to start doing experiments to try to prepare as many of these unknown crystal forms.

You don't know how many they are going to be and/or what conditions you need to prepare them. So, there's a huge variety, almost an infinite variety of conditions that are possible to do that and I think we have.

Q. Yes. Can we go to slide nine?

A. So, these are just some of the techniques that are possible for exploring this crystal form landscape, as I call it. And I said sometimes they use, sometimes it's a polymorph screen or polymorph landscape is used as a synonym. But, the method that Dr. Steed and Dr. Metzgar talked about essentially concentrated in the first line here where they talk about solution crystallization.

And even in that there's a huge variety of solvents with temperatures, whether you stir or not, and when the

solution, the crystallization is generally carried out by cooling. So the cooling rate can be a major factor in determining what you get.

Seeding is a procedure by which you add a material, usually of the same compound, in order to try to induce crystallization. An anti-solvent if you add another solvent to a solution in which the anti-solvent is a solvent in which the material does not dissolve and that induces crystallization. And all of these methods, all the changes in these methods can lead to different crystal forms.

But, that's only part of the story because all these other techniques are used to explore the crystal form landscape.

Q. What is the timeframe needed for these experiments?

A. Well, some of these experiments can be done in a matter of minutes or hours, or some of them, especially if you'd like to see what happened over a period of time, it can take months. And that's demonstrated on the next slide, I think.

Q. Slide ten?

A. So, some on the upper, on the upper part, you see we have some of the techniques for generating crystals from solution which I just talked about. And the ones in yellow are just some of the others that were on the previous slide.

And the time scale at the bottom goes from the relationship between the time necessary to reach one of these

techniques on an approximate level, of course, and it goes anywhere from seconds to months.

And sometimes if we're interested in investigating metastable polymorphs or trying to find metastable polymorphs where you generally try to do those rapidly, and the more stable ones we try to get more slowly.

These are just general guidelines. That says nothing about any particular compound that we might be looking, we might be investigating.

Q. You mentioned that defendants' experts had focused on solution crystallization techniques. You mentioned that there's a huge variety of conditions that can be varied. You talked about some of them.

Are there more examples of conditions that can be varied in the literature?

A. Yes. That same paper we saw by Morrissette a few minutes ago has a table. That's the same paper.

Q. I believe it's at page 3.

A. And this table demonstrates a very busy table because there's a lot more information. There are a lot of ways to do it. It's hard for me to point, but, I will try to describe it.

See the heading in this table is Crystallization composition and processing variabilities. So, this delineates in a very general way some of the possibilities and some of the variety of techniques that might be used in trying

to prepare crystal forms.

If you concentrate on the left-hand column, the one right there, so that's, we are talking about polymorphs and solvates for the moment. And so if you go down, you see solvent combinations, degree of super stauration. Super saturation is a concept where you're actually dissolving more material in the solvent than the solubility. And that's done by heating it up.

And then you can add materials that says anti-solvent. And you can add the additives that you can also put in other materials into the solution. And so those are, those are just the kind of things you can do in solution crystallizations.

And then if you go over to process variables, so then for each one of those there are different possibilities whether methods are whether thermal, they are heating or you add an anti-solvent or you evaporate it or do a slurry conversion or other variables.

And you see the table, there's an entry in every box, so to speak. And each one of these entries then has a huge variety of possibilities for changing the conditions.

Q. Did you hear Dr. Steed testify that the Byrn reference provides a systematic well-defined approach to carry out an investigation to determine polymorphism?

A. Yes, I did.

Q. Do you agree with Dr. Steed?

A. No, I don't.

Q. Why not?

A. Well, what Steve Byrn tried to do was to summarize, in a very exact way, sort of a root decision tree it's called, for how one might look at it. And he has one entry on the upper left-hand corner of this decision tree which says polymorphs found. And then there are 3 or 4 lines of the kind of conditions that you might try.

And that 3 or 4 lines actually summarizes everything we've been talking about on the last couple of slides.

Q. Are there any shortcuts involved in the crystal form screen?

A. Nope. You just have to do the experiments. There's no other way to determine what the crystal form landscape looks like. You just have to do the experiments.

Q. And in 2004 was there a standard set of screening experiments that Tapentadol could have been plugged into?

A. No. There wasn't then and there is no standard recipe now.

Q. If a crystal form screen had been conducted on Tapentadol, would a person of ordinary skill have any reasonable expectation of discovering the monoclinic form?

A. No, they wouldn't. The whole point of doing the experiment is you don't know what the result's going to be.

Q. In our case form A was discovered relatively quickly,

right?

A. Yeah, but that's hindsight. That's the only way. We only know that because that's what happened. But, there was no way of knowing that before the experiments were done.

Q. And here there's only polymorphs A and B, right?

A. Right. That's also hindsight. There could be more. But nobody could tell, prior to carrying out the appropriate experimentation, what the crystal form landscape would look like.

Q. Is there any guarantee of obtaining the absolute most stable form of a given compound if you do a crystal form screen?

A. No, there's no guarantee. As I pointed out from mentioning Oswald's rule and Glaxo didn't discover the second form of hydrochloride and Abbott didn't discover the second form of ratonivir until rather late in the game.

And there's no reason to believe that other crystal forms and therefore more stable crystal forms aren't out there lurking and waiting to be discovered.

Q. So, if you were to spend a lot of time and do a polymorph screen, would there be any guarantee of finding all the polymorphs for a given compound?

A. No. You could do a thousand experiments and not find anything. And then a thousand and first might be the one that gives you, you hit pay dirt. There's just no way of knowing.

Q. Did you prepare a slide summarizing your opinion regarding the nonobviousness of Tapentadol hydrochloride?

A. Yes, I did.

Q. Let's go to slide 11.

A. This slide sort of shows how these principles apply to form A of Tapentadol hydrochloride. So, what's in the '737 patent? The '737 patent has a very, very large array of molecules. And that's what is shown. Each one of these dots or colored dots is a compound.

And as I said, some of those have been marked. And actually, actually there's a table that describes the potential therapeutic use of those. So, those are marked with numbers. I don't know if you can see them on the screen there.

So, that's what's in the '737 patent. There's no more than that. Nothing about the crystal forms. And then from that set of compounds, Tapentadol hydrochloride was chosen. And again this still has nothing to do with the crystal forms. And then what happened, we just talked about the polymorph screen.

So, we have to carry out the polymorph screen. You don't know anything beforehand. And you have the possibilities, as I pointed out, of hydrates, solvates, polymorphs and even amorphous forms. Amorphous forms don't have that same three dimensional arrangement, regular arrangement, sort of like chewing gum. That's what the

polymorph screen involves. And again you don't know any of that before you start out.

And then the question is how many. That's not known before you start out. And there are six arrows here. But, that's still a big question mark. And out of that possibility, you get a certain number. And then you have to determine their structures and their properties. And out of that number, there were two here.

So that's why the arrow leads, the arrow from two leads to structure and properties and then from that we want to know which is the most stable. And it turns out form A is the most stable.

So that's sort of a summary of the kind of experimentation that you have to carry out in order to get the form A starting with the '737 patent. And there's nothing, there's nothing known. All those steps are experimental.

Q. What does all of this lead you to conclude about the obviousness of form A of Tapentadol?

A. Well, clearly there's nothing on the left-hand side in the Buschmann family, there's nothing obvious about the eventual result of obtaining form A.

Q. I will move on to another topic.

Doctor, have you testified about inherent anticipation of crystal forms before?

A. Yes, I have.

Q. And what is your understanding of the standard for inherent anticipation?

A. My understanding is summarized on the next slide.

Q. Okay. This is slide 12. Would you just give us a summary of your understanding?

A. Sure. It says in order for something to be anticipated then whatever we're talking about must necessarily and inevitably flow from the practice of the prior art. If you carry out the, if you carry out the prior art, you have to get it all the time without exception.

And the second reference there involved the same compound I was talking about before, the ranitidine hydrochloride and Zantac.

Q. Were you in Court for Dr. Steed's argument that form A is anticipated by the '737 patent?

A. Yes, I was.

Q. And do you agree with Dr. Steed's conclusion that the '364 patent is inherently anticipated?

A. No.

Q. Let's see where the point of disagreement is. Defendants' experts argue that example 25 will always yield form A. Do you agree with that?

A. No.

Q. Okay. Why not?

A. Well, because Marita Mueller did at least faithful

reproductions of example 25 to prove that what you get when you carry out example 25 is form B.

Q. And were the samples from Marita Mueller's experiments analyzed by x-ray powder diffraction or XRPD?

A. That's how the proof that they were form B was established.

Q. Did you review the XRPD patterns associated with those samples?

A. I did.

Q. Let's go to slide 13.

Doctor, can you tell us what the two patterns are shown here?

A. Sure. There are two, the XRPDs. XRPD is a fingerprint. Just like human beings have fingerprints, solids have fingerprints. And the way we determine the fingerprints is by measuring the x-ray powder diffraction. And the lower, the lower trace in this graph is the fingerprint of form B. And it says calc. It's calculated. And that can actually be calculated from the single crystal structure which is described also in the '364 patent. So that's sort of a gold standard.

And then we want to compare the product of Marita Mueller's reproduction of example 25. And that's the upper curve. And you can see there's a precise 1 to 1 correspondence, that is to say the fingerprints match. The two points here where the arrows are just have to do with a little

bit of aluminum is added in here to make sure that this whole trace is calibrated. So they have nothing to do with the sample that was in there.

Q. Did you see any form A in this sample?

A. No, there is no form A here. And we can, we can determine that and what we do when we start to measure these things and look at them and become familiar with them, like I said, we determine that there are a lot of peaks here and a lot of lines that can be very confusing.

But, those of us who work in this field very quickly recognize that there can be certain markers that we can use to determine it. And sometimes these markers appear sometimes in the patent descriptions.

So, form A we learned if we look at form A in a moment we will see a little bit of form A. Form A has these two peaks here. And you can see that they come at what we call windows. They come at places where form B doesn't exhibit any intensity.

And so there's an easy marker for us to determine. If we look at those particular places, which is actually if you look at the X scale, the X scale is a two theta value the way the experiment is carried out. And so the two theta values form A which are representative, there are others, but these are the two that we would normally look at to see if any form A is there. Then the two peaks are 18.9 and 22.5. And there's no trace in them at all.

So this form is pure. This material that Marita Mueller prepared is pure form B with no trace of form A.

Q. All right.

MS. RANNEY: And for the record, Dr. Bernstein is pointing to two arrows indicating form A at X value 18.9 and 22.5.

Q. All right. Could we keep slide 13 and put below it Figure 4 of plaintiff's Exhibit 1458? If we can zoom in on figure 4 a tiny bit so the scales are more similar.

Doctor, do these two patterns appear as essentially the same to you?

A. Yeah. Figure 4 from the patent, and this is the same form, this was the same pattern on the lower figure that appears in the upper figure, both calculated and experimental.

Q. Okay. Let's go to slide 14. Maybe we will call out the key at the top there.

What are the two pattern shown here, doctor?

A. Well, it's difficult to see it with the blue on it. But there's a sort of purple line and a black line. The black line, as it says, is form A. And the purple line is form B as you'll see. We can look at the arrows.

Q. Let's take the key off so we can see a little better.

A. Okay. So now you can easily see that, where in the previous where we had windows here, there's form A and there's a peak there. And there's a peak there. So that's how we

usually recognize it.

Whereas the two characteristic form B peaks are here and here where their windows then inform -- I'm having a hard time pointing, but, this one points down. There's nothing in form A there. And there's nothing in form A there.

So that's how we can easily determine if any solid contains all A, all B or a mixture of the two, if we see the peaks for both of them.

MS. RANNEY: For the record, Dr. Bernstein was pointing to 2 arrows indicating form A peaks and pointing to the purple line and also pointing to 2 arrows indicating form B peaks.

Q. Doctor, just to clarify, this purple pattern is the XRPD pattern for the first of Miss Mueller reproductions in example 25?

A. The purple one, yeah.

Q. Yes?

A. Okay.

Q. Is that a yes?

A. I didn't say that.

Q. Yes. I just wanted to clarify.

A. Okay. Yeah. Right. I mean you can see it's B. It's marked as B. But the caption is a little difficult to read.

Q. Let's go to the next slide, slide 16.

Have you reviewed this pattern, doctor?

A. Yes, I have. And this one is GBBU 322-1-3 which is Marita Mueller's third reproduction, example 25. And so there's -- and the x-ray powder diffraction pattern is on the purple line here. And the lower curve is again form A.

And now if we put in the arrows, you can see it's a little bit difficult to see. But, I will try. I'll try.

Q. Feel free to come up here if that's easier.

A. I will try to point out. May I, your Honor?

THE COURT: Yes, please do.

A. So, as I said, this is Marita Mueller's, the trace of the x-ray powder diffraction pattern from Marita Mueller. And the lower form, the lower trace is form A. And here's the one characteristic peak of form A and it comes through right to here. So you can see it.

And the other characteristic peak that we use sort of as a marker comes through right here, okay. And you can see on form, on the trace from Marita Mueller's material, there's no, there's nothing here and there's nothing here. But, the form B peaks are very strongly represented both here and here.

MS. RANNEY: For the record, Dr. Bernstein was pointing to peaks form A in the bottom blue pattern. Then pointing to the absence of those peaks in the top purple pattern.

Q. Did you hear Dr. Metzger testify that this XRPD pattern is too noisy to determine whether form A is present?

A. Well, it is noisy. And I mean it is what it is. And that's what sometimes when we do an experiment like this, sometimes the traces are noisy.

But, it's, I think a person of skill in the art or anybody even actually in this room can see that there's no, that they, even so, there's no A here and that the trace is a trace of B in the x-ray powder diffraction pattern of Marita Mueller's example.

Q. If there were form A in this sample, would you expect to see predominant peaks at the indications you've indicated?

A. Yeah. I would expect to see peaks. I would expect to see peaks in the purple trace where the arrows are indicated because those are two of the strongest peaks. So they would come up first if there's a small amount of impurities of A in there.

Q. Okay. Have you reviewed Dr. Roush's opinion regarding Miss Mueller's reproduction of example 25?

A. Yes, I have.

Q. Do you agree with Dr. Roush that Miss Mueller's experiments were faithful reproductions of example 25?

A. Yes, I do.

Q. Do you recall Dr. Metzger and Dr. Steed's criticism that Miss Mueller's reproductions produced Tapentadol that was the wrong color?

A. Yes, I do.

Q. And do you agree with defendants' experts that this suggests that Miss Mueller did not faithfully reproduce example 25?

A. No, I don't think the color indicates a level of impurities that could effect this. And there are actually two pieces of experimental evidence that indicate that. One is that the NMR, the nuclear magnetic resonance spectra of the material didn't show any impurities at a level that was detectable, at least by NMR. So, a very high level of purity. And the x-ray powder diffraction pattern doesn't show any evidence of any impurity.

I would like to add, I mean, a color, I have dealt with color since the days of my Ph.D. thesis. As I said my Ph.D. thesis was in spectroscopy. And we learned very early that color is a very interesting phenomenon. And these organic materials at very, very low concentrations can be colored.

So, even one part in 10,000 might add a slight yellow or orangeish tint to the sample and not be considered an important chemical or solid state impurity.

Q. Does the '737 patent specify specific color requirements for example 25?

A. No, it doesn't.

Q. On similar lines, do you recall Drs. Steed and Metzger testifying that Miss Mueller's reproduction of example 25 led to examples that were impure?

A. I heard them say that.

Q. Did this criticism effect your opinion that Miss Mueller faithfully reproduced example 25?

A. No. The x-ray powder diffraction patterns clearly show that for 1-1 and 1-3, that she got form B.

Q. Does the '737 patent specify a particular purity requirement for example 25?

A. No.

Q. Did you hear Dr. Metzger and Dr. Steed testify that the only way that form B can exist at room temperature is through impurities?

A. I heard them say that.

Q. Do you agree with them?

A. No.

Q. Why not?

A. Well, I think, I don't think there was any proof. I think that was all speculation on their part. The idea of showing -- this is not a totally new idea. The idea of demonstrating that impurities can effect which crystal form you get is not particularly new. It's been looked at quite a bit.

For instance, back to the ritonavir example, Abbott really wanted to find out what was it that caused the new form. So they did a very thorough investigation of all the impurities that resulted in the synthesis of the material. It took them about 3 or 4 years to do that. And in the end they did

isolate one impurity which led to the formation of the more stable form which caused them all the problems.

But that hasn't -- Dr. Steed and Dr. Metzger didn't do anything of that sort here and form B was prepared.

Q. Did you review any documents discussing samples of Tapentadol hydrochloride at Grunenthal and impurities?

A. Yeah, there are a couple of tables that I think we have here.

Q. Let's put up plaintiff's Exhibits 1579.

MS. RANNEY: For the record, this is a translation of plaintiff's Exhibit 507.

Q. Is this one of the documents you reviewed, doctor?

A. Yes, it is.

Q. And what's shown in this table?

A. Again, this is maybe --

THE WITNESS: May I, your Honor?

THE COURT: Yes, definitely.

A. There's a lot of information here. Okay. So, there are different batches here where these are crystallization attempts. And there's a whole lot of data here. This is what was obtained.

But the important point is what, well, what's in the left-hand column and the right hand column. And you can see for instance all the entries on the left, form B was obtained and that the impurity levels vary quite a bit.

The one I'd like to point out is this one is quite low .35 percent and it's .2 percent. And the point is that BN300 and BU351 are impurities. I'm not actually quite sure of their identity. But it's just to show the level of these two impurities that were identified by Grunenthal.

So, as you can see here, so, these are low, some of them are higher. But, there's no, there's no difference in all these cases form B was obtained.

Q. Okay. Let's look at the second page of this document.

A. So, in this case in most of the cases form A was obtained, form A and a little B. And there are some of these which have higher impurities than those which were shown on the previous slide for form B.

This just says it's quite a range of variation here for these two impurities. And there's nothing really to draw any conclusion about distinguishing between form A and form B and the level of impurities here. That's the object of these two slides.

Q. Thank you.

THE COURT: I do have a quick question about the color that we were talking about before.

THE WITNESS: Sure.

THE COURT: Is there anything in the field that someone would use to analyze and determine what to call a specific color? If they observed something after an experiment

and they had to make a determination as to whether it was yellow, beige, white, cream, is there some sort of ranking system to determine how you address that color?

THE WITNESS: Not really. If you go through the -- you're saying to actually make a quantitative description of the color?

THE COURT: Or a qualitative assessment as to what color is. How would someone actually approach the issue and determine what to write down as its color. Is there any benchmarks for doing that?

THE WITNESS: No. There are really no standards. If you go through the chemical literature from the earliest possible days, you think back a hundred, I'm actually looking at these, if you go back a hundred years, 120 years ago for organic chemists there was almost, there were no, there's very few instrumental methods to do to make measurements like this.

And so how did they, when they got a new material, how did they characterize it? Well, they measured the melting point. And melting point was one of the few quantitative measures you could get.

But then they did things, they recorded, I don't have it with me, but I actually, I just recently looked at an organic chemistry textbook from 1893. So then what do they do? They say record the color, record the smell, record the shape of the crystals because crystals can take on different

shapes and believe it or not they say record the taste.

And so for many years until about a hundred years ago they tasted them. Even there's one instance of oxalic acid which it says record the taste and in parenthesis it says poison. Even though they viewed it as poison, they wanted to experiment it.

But the color is a qualitative measure and it's difficult, isn't quantified. It's not quantified classically. And I am not aware of anywhere in the chemistry literature that it's --

THE COURT: That has some sort of rubric for color?

THE WITNESS: No, not at all. I mean there are colors and somebody might describe it as, you know, bright yellow or pale yellow, orange yellow, reddish yellow. And that's just the way it is. It doesn't --

THE COURT: Thank you.

THE WITNESS: It doesn't get any better than that.

THE COURT: Thank you.

Q. All right. Just to sum up our discussion of the table we were just looking at, plaintiff's Exhibit 1579, Dr. Bernstein, did you hear defendants' expert's suggestion that the form B samples tend to have higher impurity levels than form A samples?

A. I did.

Q. Do you agree with them?
A. No, I don't. I don't think they provided any evidence to prove that.
Q. Do you recall Dr. Steed testifying regarding a synthesis of Tapentadol hydrochloride conducted at the University of Wisconsin?
A. Yes, I do.
Q. Do you agree with Dr. Steed that the University of Wisconsin faithfully reproduced example 25?
A. No, I don't.
Q. Why do you disagree?
A. It's my understanding that a faithful reproduction --
MR. ALY: Your Honor, we object. It's beyond the scope of the report. This expert didn't opine on the reproduction steps and relied on another expert, Dr. Roush, who plaintiffs will be calling.
THE COURT: Counsel.
MS. RANNEY: That's true he did rely on Roush and he will be relying on Dr. Roush for his testimony. He did opine in his reports, I am happy to point you to those sections, on certain aspects of those reproductions. And those were independent conclusions he drew based on Dr. Roush's testimonial.
MR. ALY: Again, the reliance is on Dr. Roush for the testimony. So I think it would be inappropriate because we

wouldn't be able to question the basis with this expert for the expert to introduce that opinion.

THE COURT: Although you still could do the cross on that as to the extent of what the defendant did himself or knows himself versus what he relied upon.

MR. ALY: That might depends on the scope of the opinions. But, going back to the scope of the report in terms of the Rule 27, it just refers back to Dr. Roush and it doesn't say here is any independent analysis that had been done. And Dr. Roush is a witness they are calling tomorrow. So it's not like they won't have the opportunity --

THE COURT: Is there any independent analysis of this issue in the report?

MS. RANNEY: He explains what Dr. Roush has opined in his report. And then he explains why in his opinion that would not be a faithful reproduction.

MR. ALY: Maybe if Counsel could direct us to where that is and we will take a look.

MS. RANNEY: Absolutely. I believe he discusses reproductions by Organix in paragraphs 84 to 88 and Wisconsin starts at 97. It sort of refers partially back to the Organix analysis.

Your Honor, would you like a copy of his report?

THE COURT: Thank you. If you have a copy, I will take a look at it. Although maybe after looking at it Mr.

Aly might be satisfied.

Mr. Aly, do you have a copy in front of you?

MR. ALY: We are looking at an electronic copy. It looks like maybe it depends on the question, your Honor, because it looks like it's not about the procedure as a whole, but some certain aspects of the results. And that would be fine, just as Dr. Steed had done.

But, that question the way it was phrased was asking about a broader scope of it.

THE COURT: I will take the report just in case we head into difficult territory ahead. But, I think we could probably agree that if the question is rephrased, depending upon where this is in here, let me just take a look, then I think Counsel can go forward and you can do cross on the issue.

MS. RANNEY: Just to clarify, he will just be talking about this at a very high level based upon what he understands from Dr. Roush.

THE COURT: What is the page you are referring to?

MS. RANNEY: I'm not sure of the page. Number 1 starting in Paragraph 97.

MR. ALY: Page 49, your Honor.

MS. RANNEY: I believe those paragraphs refer back to earlier paragraphs.

THE COURT: It's an imbedded analysis. Yes, you

have to go back throughout the whole document. I think why don't we do this, because it does seem that there is some support for moving forward. Why don't you rephrase the question. Go ahead. To the extent there's any issue, you can go into it on cross. Mr. Aly?

MR. ALY: Okay. Thank you.

THE COURT: Thank you. Go ahead.

Q. Dr. Bernstein, did you review Dr. Roush's opinion regarding Miss Mueller's -- sorry, the University of Wisconsin's synthesis of Tapentadol hydrochloride?

A. Yes, I did.

Q. And based on Dr. Roush's opinion, do you agree with defendant's experts that the University of Wisconsin faithfully reproduced example 25?

A. No, I don't.

Q. Okay. Why not? And if you could just point out where you are relying on Dr. Roush's opinion, that would be great.

A. Dr. Roush, I assume, will opine on the synthetic details. He's a synthetic organic chemist. I am not a synthetic organic chemist. But, it's my understanding that a faithful reproduction of a patent means going back to the beginning of the patent and starting from where the inventor started in order and describe the synthesis.

And Wisconsin did not do that. And that's why I don't believe that that's a faithful reproduction. And that's

essentially why I don't believe it was.

Q. Thank you. Did you hear Dr. Steed testify that the University of Wisconsin performed the last step of example 25 and the last step is the only one that's relevant?

A. I heard him say that.

Q. Does that change your opinion that the University of Wisconsin did not faithfully reproduce example 25?

A. Not at all, for the same reason I just said. The last step is not going back to the beginning of the procedure as the inventors did.

Q. Why might it matter if one doesn't go back to the beginning of the procedure?

A. Well, if you go back to the beginning, then you have, you use the same starting materials and you carry those all the way through the synthesis and that can seriously effect the nature of the final product. And that's the principle. And as I said, Dr. Roush can describe the intricacies and the details of those procedures. But, that's the principle that I understand.

Q. Can you think of a real world example that shows why it's important to go back to the beginning of a procedure?

A. Yeah. Well, I mentioned the ranitidine and hydrochloride case. It's a bit of a story, but I will be happy to tell it.

Ranitidine hydrochloride was prepared first in 1977.

And as I mentioned, 1981 the second form appeared. And the second form was the one that Glaxo was using in Zantac and in which became the largest selling drug in the world in 1991. And so the patent on the first form was going to expire in 1995. And the patent on the second form was going to expire in 2002.

So, many generic companies wanted to try to get on the market in 1995 with form one, the first form. And they tried to prepare, they tried to prepare form one by actually taking Zantac from the market, which was form two, and then using some appropriate chemistry on it. And they always got, they always got form two back.

So, there was, if you go back to the -- I don't know if you want to go back to the slide, but I mentioned that Glaxo Novopharm case that I mentioned, okay. And so what they did --

Q. Slide 12.

A. They took the generics, they wanted to take it off the market. They went to actually six organic chemists and they said carry out example 32. That's this case on the bottom, the lower one, okay. This involved also inherent anticipation.

And what they tried to do, they said well, we want to make form one. And they tried to make form one according to the recipe in the form one patent and got form two. They got form two all the time.

They said well, if you get form two all the time, form two is inherently anticipated. So, therefore, the form two patent which was due to expire in 2002, should not be valid.

And I mentioned I was involved in that case as a witness, the first case. So I'm sort of intimately familiar with it. And in order to prove that the lack of inherent, that there was no inherent anticipation, there were two possibilities, one was to go back to the notebooks of the original inventor of form one from 1976 and 1977 and compare those with the patent. And that was done. And so there were three cases there.

But, at the same time the witness for Glaxo was Sir Jack Baldwin, the Professor of Organic Chemistry at Oxford. And what he did was he took the patent and he gave it to two of his post doctoral Fellows, his most senior post doctoral Fellows and he says you see this, take this patent and go back to the beginning. Don't go to example 32. Go back to the beginning. Start from the beginning and make it just the way the inventors did. And they did. And in June of 1993 they actually made it and they got exactly what was described in the form one patent.

So, this, so the whole idea was that they went back to the beginning of the procedure and proved that if you carry out the procedures from the beginning, you get form one. And that to me was the lesson I have carried with me ever since. So,

this is why I'm claiming that's what has to be done in this instance as well.

Q. And, doctor, have you seen any evidence in this case that a faithful reproduction of example 25 necessarily and inevitably yields form A?

A. No.

Q. Did you hear Dr. Steed's testimony that form B does not persist at room temperature?

A. Does not persist at room temperature?

Q. Does not persist.

A. Yeah, I heard the testimony.

Q. Do you agree with him?

A. No.

Q. Why not?

A. Well, there are a number of examples of form B persisting at room temperature. And batch 0 is a perfectly good example. But, Grunenthal has prepared others which still exist at this point. So, there's no, there isn't an absolute necessary transformation to form A of form B at room temperature.

Q. And, similarly, did you hear Dr. Steed testify that form B is unstable?

A. I did.

Q. Do you agree with him?

A. No, form B is not unstable. Form B at room

temperature is metastable with respect to form A.

Q. What does it mean to be metastable?

A. Well, metastable, I think we have a slide.

Q. We do.

A. So I can illustrate this.

Q. If you go to, I think it's slide 18.

A. Right. So, this slide demonstrates the idea of relative stability. So, we have these two lakes and representatives of form A and form B. And form B is at a higher elevation.

So, when we talk about energy, that's at a higher energy than form A. But this situation will be maintained as long as none of the water can get out of this high lake and drop down.

So, in terms of that we are discussing now form B is metastable or the lake is metastable with respect to form A. But, in order for form B to get out then we somehow we have to get the water over this. We have to get the water over this peak or this block or this dam or whatever it is and that would be required in order for the water to go downhill.

So, form B again is metastable with respect to form A. And that's the analogy that we use now for these two forms of the compound.

MS. RANNEY: For the record, Dr. Bernstein is pointing to slide 18 and indicating that in order to convert

from form B to form A, it would have to go over a little peak mountain that's indicated on the slide.

Q. Can you think of examples of other compounds where a number of forms exist in ambient conditions and they don't convert to the more stable form?

A. There are many but perhaps the classic one was a compound called ROY which -- ROY, R-O-Y. They are usually written with capitals letters in red, orange and yellow. And there are about 7 or 8 polymorphs known.

And they all essentially exist at room temperature, even though one of them, only one of them can be the most stable form at room temperature. And that's, and the rest of them are metastable, but they don't convert.

Ranitidine and hydrochloride and the same as I mentioned are two forms and they are actually very close in energy. But, they can exist, co-exist next to each other essentially forever. There's no transformation from one to the other.

Q. You've testified that you've seen samples of form B that existed at room temperature. And you mentioned a sample called batch 0.

Have you reviewed any XRPD patterns for batch 0?

A. Yes, I have.

Q. If we can go to slide 20. This is plaintiff's Exhibit 599.

Do you recognize this XRPD pattern?

A. This is an XRPD pattern of batch 0.

Q. How did this XRPD pattern come back?

A. As I said, Grunenthal had raw data of this XRPD pattern, which draw data means that what we have is a number of values measured along the X fact. This is the variable, the instrumental variable. And then you measure the amount of x-rays that come out of the sample which is the intensity here which is essentially the number of counts of x-rays that reached the detector.

And so those data can be plotted using Excel and I had those data plotted and this is what comes out.

Q. All right.

MS. RANNEY: And for the record the data from which this plot came from is plaintiff's Exhibit 574 and plaintiff's Exhibit 601. And those were two of the data files that Dr. Gruss reviewed last week.

Q. Okay. Dr. Bernstein, what was your conclusion in reviewing this pattern for batch 0?

A. Just so we have to do the same kind of analysis we had done previously. We have to look for the representative peaks. So, if we look for the peaks, if we want to show it's form A, form B, then there shouldn't be pure form A. There shouldn't be any peaks of form B. And there's a reference where we would expect peaks of form A if there's any impurities of form A in

here and there are none.

Again, for form B peaks appear very strongly. And in order to demonstrate this even more clearly, there's an expansion of this so you can see it I think on the next slide.

MS. RANNEY: For the record, Dr. Bernstein was pointing to areas of the pattern where there's arrows indicating where form A should be.

A. So now simply the X scale has been expanded on for this batch 0. So, we're going for over a much narrower range just to show the detail and the places where you expect to see peaks of form A if there is any there. They don't show any of that. And again the form B peaks, characteristic peaks are there.

So, this shows that batch 0 doesn't contain, is pure form B and doesn't contain any form A.

Q. And we're on slide 20 which is plaintiff's Exhibit 600. And this is just a blow up of plaintiff's Exhibit 599. So it comes from the same data files.

What do these XRPD patterns show you about the stability of batch 0?

A. What do XRPD patterns?

Q. Show you about the stability of batch 0 at ambient conditions?

A. If you measure the XRPD patterns and you see only form B, then it's stable at least until the time you measured it.

Q. Do you recall when batch 0 was synthesized?

A. I believe batch 0 was synthesized in 1994.

Q. Do you recall when the XRPD pattern was measured, roughly?

A. I think this one was somewhere around 1998 or 2000, 2002. I don't remember exactly. But at least four years later, maybe 6 or 7 years later.

Q. Okay. Do you recall a 2009 synthesis of Tapentadol hydrochloride conducted by Marita Mueller?

A. Yes, I do.

Q. Did you review an XRPD pattern for this synthesis?

A. Yes, I did.

Q. Let's go to slide 22. This is plaintiff's Exhibit 486C, Page 12. Is this the XRPD pattern you reviewed regarding the 2009 synthesis?

A. Yes, it is.

Q. What are the two patterns shown here?

A. The red is a reference for the form B pattern. So that's the upper one in this case as opposed to earlier ones where it was the lower one. And the lower, the lower one is the x-ray powder diffraction pattern of the 2009 synthesis by Marita Mueller of form B. And you see that it's an excellent match with no form A peaks there.

Q. Have you indicated where the form A peaks would be on this?

A. Yeah. I think we have the arrows to show where we

would expect the form A peaks if there was any form A. So there they are and that's again clean.

Q. Thank you. Have you seen other examples of form B that existed at room temperature besides batch 0 and PG 1026 that are shown here?

A. Yes, there are others.

Q. Having reviewed these XRPD patterns and those other samples you mentioned at Grunenthal, what did you ultimately conclude as to whether the claims of the '364 patent are anticipated?

A. That the claims of the '364 patent are valid.

Q. Let's move to defendants unclean hands allegations.

Did you hear Dr. Metzgar testify that Grunenthal acted with unclean hands indicating the '364 patent?

A. Yes, I heard him testify to that.

Q. Do you agree with him?

A. No, not at all.

Q. Let's walk through these allegations.

Did you hear Dr. Metzgar testify that Grunenthal acted with unclean hands because it's not preserved relevant samples of Tapentadol hydrochloride?

A. I heard him say that.

Q. Do you agree?

A. Not at all.

Q. Why not?

A. First of all, there's no, there's no necessity to keep samples around for many, many years. We don't necessarily do that or we didn't do that in my laboratory. My laboratory doesn't and Beer Sheva doesn't exist anymore. But, we didn't keep them around and they didn't either.

And even more so they didn't have to. But, even more so when this was declared a controlled substance, they had to clean the lab out. So, they couldn't keep them around. And I don't see any intention to misrepresent anything to the patent office.

Q. Could we put up plaintiff's Exhibit 1458 patent. Let's go to Bates Number 57600 and go to example two.

Did you hear Dr. Metzger testify that Grunenthal misled the PTO about the starting materials used in example two and other examples in the '364 patent?

A. Yes, I did.

Q. Do you agree with Dr. Metzger?

A. No.

Q. Why not?

A. Well, this is, if you go, actually, well, the example two is preparation of form A(1). And if you look at the procedure here, this is, it starts out by saying the compound was synthesized, was prepared according to example 25. But, this is a recrystallization experiment.

And in order to carry out a recrystallization, you have

to dissolve the material. So, it doesn't matter where it came from. And, moreover, it refers to European example 25, the European patent. And somebody reading this patent, if the material wasn't on the market for sale by some commercial company, they would have no other way of knowing how to get the material.

So, they would have to go and prepare it. And that's what's described here. But no more than that. Just how to get some of this compound so you could dissolve it and do the recrystallization.

Q. All right. And do you recall Dr. Metzger testifying that Grunenthal believed that example 25 will always produce at least some form A?

A. I heard him say that.

Q. Do you agree with him?

A. No.

Q. Why not?

A. I haven't seen any proof that that's the case. You get form B. You get the batch 0. And others you get they are pure.

Q. Okay. Let's go back to slide 14.

Do you recall discussing this sample earlier?

A. Yeah.

Q. And is it your testimony or was it your testimony that this is a pattern from Marita Mueller's first reproduction of

example 25?

A. First reproduction, that's the 1-1 right in the upper left-hand corner.

Q. What form does this XRPD indicate that that sample was?

A. I didn't hear.

Q. I'm sorry. What form of Tapentadol was Miss Mueller's sample from this reproduction?

A. Form B.

Q. And is there any form A present?

A. None whatsoever.

MS. RANNEY: Thank you, Dr. Bernstein. That's all my questions.

THE COURT: Thank you. Mr. Aly.

MR. ALY: Yes.

THE COURT: Do we have an estimate as to time?

MR. ALY: Over an hour. Shall I start today?

THE COURT: Would you like to take a break and then maybe we'll try some of it?

MR. ALY: It's up to your Honor. I'm good either way. We are handing out binders. That will take a couple of minutes.

THE WITNESS: I could use a break.

THE COURT: That's fine. Why don't we take a five-minute break and then we will start at least some of it to cover some ground.

Does that sound good or would you folks like to break for the day?

MR. GLANDORF: Our preference is to take a break and continue. We have Dr. Roush.

THE COURT: I'm trying to get the schedule moving forward. All right. Let's take a five minute, ten minutes. We will come back and we will see how much we can actually get done. Thank you.

(Whereupon a short recess was taken.)

THE COURT: Have you had an opportunity to take a look at the exhibits?

MS. RANNEY: Yes, we have. We have a translation issue with defendant's Exhibit 1332 and we're just locating plaintiff's competing translation. And also defendant's Exhibit 1106, we have a competing, another translation. There are a few things in this exhibit that have been obscured. And I believe we have already spoken with the defendants and think they are going to use our version.

THE COURT: You said --

MS. RANNEY: They are going to use our version which is plaintiff's Exhibit 511.

THE COURT: For both exhibits or just the one?

MS. RANNEY: We're still locating our translation of defendant's Exhibit 1332. Hopefully we will get that done soon.

THE COURT: Okay. Mr. Aly, are you using the exhibit on the translation on one. Is that it?

MR. ALY: Well, it looks like they are saying one of our exhibits, DTX 1106, we should use 511_T instead. That's fine. And for the other one 1332, they are identifying an issue with another document.

But, whatever that other document is, we can have both available. I don't think it comes down to a translation issue.

THE COURT: How does that sound?

MS. RANNEY: That sounds fine. Thank you.

THE COURT: That's fine. Any demonstratives?

MR. ALY: Only the one.

THE COURT: I think we're good to start. Let's begin, please.

MR. ALY: Thank you, your Honor.

THE COURT: Thank you.

CROSS EXAMINATION BY MR. ALY:

Q. Dr. Bernstein, thank you for your help with this case. You have been an expert in many other cases before this one. Is that right?

A. That's correct.

Q. In fact, over 25 cases you have been an expert, right?

A. It depends how you define how many cases. I've been, as you know, at various levels. I haven't testified in court

in 25 cases. And I am not sure I've been deposed in 25 cases. But, I just don't know the number. The number of 25 sounds a little bit strange to me.

I may have been retained on that number of cases, but I don't, I don't, not all, certainly not all of them went to Court.

Q. In terms of the number of expert reports you've submitted on polymorph patent issues, it's been in over 25 cases. Is that fair?

A. I have never counted it. I really, it could be, but I have never really counted it.

Q. And let me make clear on this, regardless of the number, each and every time that you've submitted an expert report it's been on behalf of the patent owner.

Is that correct?

A. That's correct.

Q. And each and every time you've provided an opinion, an opinion submitted in a case or in court or in a deposition, it's always been that the patent is valid. Is that true?

A. If the question was validity, that's true, yeah.

Q. Now, you did talk about a book that you had authored, right, on direct examination?

A. One book. It's a book, yes.

Q. I think you have a copy of that book as well?

A. I have it here.

Q. I'd like to go through some of those pages to sort of set the themes that I would like to discuss with you over the course of the examination. So that's PTX 1041?

A. Sure.

Q. Let's start at Page 252. And Page 252 appears, does it not, Dr. Bernstein, in a section you have discussing metastable polymorphs?

A. Okay.

Q. Is that right?

A. That's the section. That's Section 7.6.

Q. On Page 252 in the bottom paragraph, we can zoom into that. The first sentence you write is that one traditional strategy for screening a compound for polymorphic behavior involves the trial of a variety of solvents and solvent mixtures.

Do you see that?

A. Yeah. One traditional strategy. That's correct.

Q. You agree that doing a polymorph screen is a traditional strategy as of the time you wrote the book in 2002, right?

A. No. I agree with that. But, the sentence says One traditional strategy involves, one strategy involves a trial of a variety of solvents and solvent mixture.

Q. And the idea that you were discussing during direct examination is the result of the screen, one may not be able to

predict ahead of time. Is that right?

A. That's correct.

Q. But the screen itself, you're not saying that in this case Grunenthal was the first person or first entity to do a polymorph screen, right?

A. No.

Q. And in fact when you wrote the book, you went on to describe, in the second sentence, that our understanding of the role and choice of solvent has improved considerably because of the state of the art by that time, correct?

A. At that time it had improved considerably over the previous hundred years or so, yeah.

Q. And on the next page, shifting to another of the topics that you talked about on direct, you mentioned that you didn't think that impurities could stabilize a metastable form. Do I understand that correctly?

A. No, I didn't, I didn't say that. What I said in this case it had not been proven that impurities stabilized. I didn't say impurities -- there's no way that impurities could stabilize a particular form.

And I think I have written in many places that sometimes impurities can lead to a different crystal form. And that's certainly a possibility. But, what I certainly said here is I haven't seen any proof that impurities play a role in determining which form you get.

Q. Do you agree with me though, Dr. Bernstein, that impurities can make stable an otherwise metastable form at room temperature?

A. I'm not sure I agree it can make stable. The point of impurities is they can direct a crystallization to a particular form. I'm not sure I'd say the impurities stabilize a form. What might be is impurities can influence the result of a crystallization. But, I really haven't seen very many.

And, for instance, in the ritonavir case, it was the presence of an impurity which led to the crystallization. But, it wasn't that the impurities was incorporated within the crystal and stabilized it. I'm not sure I'd say -- the whole idea of an impurity stabilizing a form is contrary to the idea of crystallization. It doesn't go together.

I'm not saying it's impossible. But, my understanding of it is that impurities can influence the result of a crystallization. But, I wouldn't necessarily say that impurities stabilize it. I haven't actually seen anybody prove such a thesis.

Q. Do we agree then, Dr. Bernstein, that an impurity could help influence which polymorph results from A?

A. Yes. Impurities definitely can influence which direction a crystallization goes.

Q. In fact, in the book, this is on page 253 now of your book, you write that in some cases additives are actually

purposely put into formulations to help influence which polymorph results, correct?

A. These are called tailor made additives and they are exquisite experiments that some of my colleagues in Israel carried out. Really exquisite. Sometimes the additives, well, most of the cases where additives are used, they are designed specifically to prove a point. And I can cite, I cite papers here. But, there have been more recent ones.

So, it's generally you don't just throw in an additive, although some people do to see what happens. But additives certainly can influence it. And that's very similar to the influence of impurities where you don't know what you're adding. Here the case is tailor made additives.

Q. Then shifting to a third subject that will be one of the ones we discuss in more detail, in your book you also write about the ranitidine example. That's one of the things you talked about on direct, correct?

A. Yes.

Q. And that was the caselaw discussion that you had where it involved Glaxo?

Is that right?

A. That's correct.

Q. Were you personally involved in that case as an expert?

A. I was.

Q. So, you've got information from your involvement in the

case that really isn't public information or even case information, right?

A. Not true.

Q. So you --

A. Not true. I don't agree with that. I don't agree with you.

Q. In fact, it's also correct that you put the materials about that case that you were aware of in this book, didn't you?

A. I describe some of it and I described it elsewhere. And there's a lecture I give about that case all the time. Everything I wrote about and everything I talked about is public information and it was at the trial.

Q. But, today in court, to be clear, you said that what was wrong with the replication of the prior art in that case was that the people replicating it, started it later in the process rather than in the beginning of the process?

Isn't that what you said?

A. That's what I said.

Q. And in your book, let's see, you describe it here. Let's go to Page 298. We are still on PTX 1041. And you see on the bottom left Section 10.2 is the ranitidine hydrochloride case.

A. I'm sorry, you are on page 298?

Q. That's correct.

A. Okay.

Q. You sees the ranitidine hydrochloride case that you were talking about?

A. Correct.

Q. Now, let's go to Page 300 right where your cursor is, the bottom half of that paragraph, please.

And now here when you were discussing it, Glaxo argued not that there was a wrong starting point information, but actually that the people replicating the work were contaminated with seed crystals of the wrong form, correct?

A. You got my testimony wrong.

Q. I'm just asking what you wrote in your book.

A. That's what I wrote in my book. But, you're saying that contradicted what I said today. That's not.

Q. Let's focus on this some more. When you were talking in your book about the replication of example 32, the reason it was not a faithful replication in that case from your experience is because the experiments were contaminated with seed crystals of one polymorph instead of the other, right? That's what you wrote?

A. That's the reason they didn't get it. But, as I pointed out in my direct testimony, the reason Glaxo did get it was because they went back to the beginning, they went back to the beginning of the patent.

Q. And in particular you were focusing not, in this book

chapter when you were describing the case, on anything that had to do with the sequence of events, but, actually the seed crystals which are put in during the crystallization process. Isn't that true?

A. No.

Q. And therefore --

A. No. The answer is no.

Q. And I'm continuing with the next question, sir.

And putting in the seed crystals, that directs or also can influence the polymorphs that one gets. Isn't that right?

A. Yes. In this case, though, the seed crystals that were involved were non intentional. They weren't put in as, to use your words, they weren't put into the crystallization. But they were ambient seeds. But I want to distinguish between the two.

Q. I think you've answered the question.

A. Okay. I've answered the question.

Q. My next question, sir, is in that particular case with the seed crystal, that's different than the example 25 that we've been talking about here for a couple of weeks because there's no issue or discussion that anybody's made about seed crystals, right?

A. No. But my point was completely different.

Q. Let me ask you about the example 25, if I may. Example 25 has three steps. First step, second step, third

step. You are familiar with those, right?

A. Yeah.

Q. And the third step has a starting material, we called that the minus 23 compound. And then it's put in solution and then steps are taken after that to get to the minus 21 Tapentadol hydrochloride, correct?

A. Okay.

Q. Do you understand that?

A. I haven't gone into that in detail. As I testified, I haven't gone into it. I haven't looked at all those steps in any detail.

Q. But, in terms of crystallization, making a crystal that could be one polymorph or the other, you know that happens in the third step because it goes from solution to crystal, correct?

A. But that's different from a faithful reproduction of a patent. A faithful reproduction of a patent, as I testified, is going back to the beginning of the patent, starting from where the inventors started and going to the end. And the crystallization step is one. But, you have to have the right stuff in there in order to get the right material.

Q. And I understand your testimony on that, Dr. Bernstein. But, my question is just more focused on when do crystals form in the third step of example 25.

Is it in the beginning, middle or end of that process?

A. The material is formed at the end, but, it's formed from a solution that contains everything that's been carried along since the beginning of the synthesis.

Q. So, you believe, and let me get this right because it's an important point, you believe that when Marita Mueller did the work, she did the first step and second step and didn't have any other solids that came from that, but, it was still in solution into the third step.

Is that your testimony?

A. That's not my testimony. I think Dr. Roush is going to testify about what Marita Mueller did. What I understand is Marita Mueller in gross simodo (sic) went back to the beginning and started from the beginning and carried out example 25.

Beyond that, I said I'm not, I'm not a synthetic chemist. And I'm sure you're going to hear tomorrow Dr. Roush talk about all the details. But, that is my understanding again she went back to the beginning and she got, she got form B.

Beyond that, I haven't really examined it in any more detail because Dr. Roush is a first class organic chemist and can do it a lot better than I can.

Q. But, sir, you did offer an opinion and I wanted to find out from you if you knew one way or the other whether the minus 23, this is the starting compound for the third step in example 25, whether Marita Mueller tested that for any amount of

impurities.

A. I don't know.

MS. RANNEY: Objection, your Honor. These questions are going into a great deal of detail about the example 25 synthesis. And Dr. Bernstein has already stated that he relies on, you know, Dr. Roush is going to be the one to go into the details of the synthesis.

THE COURT: And he did plainly state that.

Are we going to go into much more of the particulars on that?

MR. ALY: No, but that was related to my objection that because of the opinions offered, I want to make sure that we understand the scope of those opinions, your Honor.

THE COURT: That's fine. Thank you.

Q. And I do understand that you're not a synthetic organic chemist, Dr. Bernstein. But, just to make sure I understand the replication steps that you were talking about, the minus 23 compound that the University of Wisconsin used to start the process of the third step, do you know if they checked it for purity?

A. I don't know.

Q. And you don't offer an opinion as to whether or not the starting material, this minus 23 for the third step, was appropriate to start because it was checked for impurities or

not?

A. If they started, they started with something else. They didn't go back to the beginning of the patent. I don't know what they had. I don't know what they, whether they checked it or not. And even if they checked it, I don't know what they got.

But, I do know that they didn't go at that time to the beginning of the patent.

Q. For Marita Mueller's work, do you know for sure whether she went back to the beginning of the patent?

A. That's my understanding. And I have read Dr. Roush's declaration. And I understand from that he says she did go back.

Q. So that I understand what I should question you on or not, are you saying, sir, that Marita Mueller did all of the steps from the beginning of where the patent starts, all the way through example 25? Or are you just saying that's your understanding based on what Dr. Roush said?

A. I have not spoken to Marita Mueller. I did not read her deposition testimony.

What I understand is I read Dr. Roush's declaration and he said she did. And that's the basis of my knowledge.

Q. Will you agree with me if Marita Mueller actually didn't follow example 25, then we shouldn't rely on her work to determine whether it's the right or the wrong polymorph?

A. I mean you have to establish the facts. I don't -- will I agree with you? I don't know. I mean I have to, that's a hypothetical. If you establish the facts and that's the case, then I'd have to think about it a little bit more.

But, I haven't seen any, I mean, I haven't seen any evidence to that effect at all.

Q. And the particular case that you were discussing which is on the slide here or on the screen here for ranitidine, there was also a purity requirement that was in the claims in that case.

Do you understand that?

A. I don't know what you mean.

Q. In other words, if there are different polymorphs that are being distinguished, did that case have a purity requirement that it had be a certain percentage of form one versus another form?

A. No, you are mixing up the cases.

Q. Well I'm asking in that case.

A. In this case, no. There were two cases Glaxo Novopharm. In the first it had to do with the validity of the form two patent. And so that was the case of polymorph identity.

In the second case Novopharm went on the market with form one. They learned how to make form one. And Glaxo then claimed that they couldn't make form one without a form two

impurity. And that was the issue in that case. And that went, also went to trial. And just for the record I was a witness in that case as well.

Q. And in this case the one we are talking about here with the '364 patent, all the claims that are asserted, not one of them has an impurity or purity requirement in the percentage of form A's that must be present, right?

A. There's no issue of purity here as far as I understand it.

Q. And you do not dispute, Dr. Bernstein, that the University of Wisconsin test did show some form A in the result, correct?

A. They showed what they showed. I haven't reviewed the University of Wisconsin results. And I don't recall ever doing that right now.

But, if they had, if they had some form A, they had some form A. They didn't -- that was not a faithful reproduction of example 25.

Q. What I want to make sure is that do you have an opinion or not whether University of Wisconsin got form A?

A. I honestly don't remember the fact. If they got form A, they got form A. I mean I can't say anything beyond that.

Q. All right. Now, we are also shifting to the batch 0.

You testified on direct examination that there was a batch 0 that had been prepared at Grunenthal. Is that right?

A. Yes.

Q. And apart from Dr. Roush's opinion, do you yourself have an opinion whether batch 0 was made by the same basic synthetic route as described in example 25 of the '737 patent?

A. I don't recall ever seeing how batch 0 was made.

Q. So, you don't have your own opinion?

A. I don't have an opinion on how batch 0 was made.

Q. And in terms of impurities, when we're looking at the forms B and A, you agree that in fact form A is the stable form at room temperature, correct?

A. That's correct.

Q. And I'd like to look at DTX 1001 to discuss the temperature effect with you, sir.

You should have copies in the binder if you need them. But right now we are looking at the cover page of the 2006 polymorph screen report that Grunenthal put together based upon SSCI's study.

A. Will I need to look at it in the folder or be able to see it on the screen?

Q. You should be able to see it on the screen. I'm just saying if you need it, it's there.

If we could turn now to Page 18 of the PDF which is the one ending in 21107 and look at Table 10. And Table 10 in the SSCI study shows what they titled a variable temperature XRPD study. You're aware of that one, right?

A. I'm not sure I understand what you mean by you're aware of them. I know that SSCI did a lot of work on this compound.

Q. Dr. Bernstein, is this temperature study one of the things that you reviewed?

A. I've reviewed a lot. I mean we've been going on, as other witnesses have said, we have been going on for a long time. I have looked at this. I'm sure I've seen it. But, the SSCI did a lot of work and I don't remember everything by heart. But, we can look at it.

Q. Sure. Thank you, Dr. Bernstein.

You see here where they've got the 32 degrees. That's the starting temperature of some material. And they say that's XRPD form A.

Do you see that?

A. Yep.

Q. And then they heat that from the 32 to 75 degrees celsius. And then that results in form B, that heating step, correct?

A. Yes.

Q. Now, they continue heating it again and then cooling it down, it remains as form B until you see this last step where it says room temperature XPRD, take it to the next state. Do you see?

A. Yes.

Q. When the room temperature is taken the next day they

see A, correct?

A. That's what it says.

Q. So, what's happening here, do you agree with me, that when you take A and you heat it up past a certain temperature, it does convert to B? But, then if you let it sit there, it should normally return to form A?

A. This is one experiment and that's what happened. But not every experiment, not every experiment when you cool, when you cool B to room temperature or even a little bit below it doesn't always convert back to A.

Q. And there's something different then obviously, sir, between the form A and B they were testing here and the form B that Marita Mueller got according to the work that she did?

A. What's different about it?

Q. I think you yourself said, did you not, Dr. Bernstein, that the one that Marita Mueller made was stable for more than overnight still as form B, whereas this one changed to form A. Do you agree there's a difference between those two?

A. There's a lot of data here in this situation. There are cases -- this is a case where A, sorry, B converted back to A at room temperature. Fine, that's one. There are cases where B doesn't convert back and instances where it does convert back. It doesn't always convert back at the same temperature, a phenomenon called hysteresis.

So, there are samples of B that have been stored at

room temperature for a long time. Batch 0 is one of them. And they don't always convert back. And that's part of the instance of metastable. There are factors which prevent the conversion from B to A.

Q. And in both cases though Dr. Bernstein, your opinion is that it's still form B, whether it converts back to A at room temperature or stays as B in room temperature, it's still the same form B?

A. B is B is B. A is A is A. There's only one B. There's only one A. And if you measure the x-ray powder diffraction pattern of B, you get that fingerprint. If you measure the x-ray powder diffraction of A, you get that fingerprint. There's no variation in B or in A. There's one B and there's one A.

Q. And, sometimes B, when SSCI did the work, for example, reverts to A at room temperature without doing anything else, just letting it cool.

A. Yes.

Q. So, with that, let's look at your demonstrative number 18 to talk through that, please. Here in your demonstrative 18 you had basically two ponds, one as form B as a higher pond and one as form A, a lower pond. Is that correct?

A. Correct.

Q. Form B, you were testifying, is the metastable form at

room temperature and the form A is the stable form?

A. That's correct.

Q. So, there's something in between the form B that is preventing it from going to form A even though A is the more stable, right?

A. Sometimes it can go, sometimes it doesn't go, as we saw on your previous slide. Absolutely.

Q. And you're aware that Grunenthal looked into this question and found that impurities are likely to play a role in preventing B from getting to A?

A. Grunenthal looked into and suggested a possibility in a presentation, an internal slide presentation in the company that impurities were a possibility. It has never been proven that impurities actually do that and, if so, which impurities might be the cause. That's a possible suggestion and that could be.

The fact of the matter is B can exist and does exist at room temperature for a long time. And nobody has proven to me what the reason for that is.

Q. And to be clear, though, on the other direction, Dr. Bernstein, no one has even put a hypothesis out there that there are impurities that could stabilize form A at room temperature . Nobody's even said that, right?

A. I haven't seen anybody, I don't see any reason why they would do it. If that's a stable form at room temperature, why

should it be? Why should it be stabilized by anything? I mean unless there's another form that we don't know about and something is stabilizing with respect to that. But A is A and A is stable at room temperature.

Q. So, let's look at some of the Grunenthal analysis here, DTX 1060, please.

Do you see here, if we can get the date, Mr. Haw, this is the September 2001 study of the status of polymorphism research that SSCI had done, correct?

A. Yes.

Q. And if we can go to the text of the letter underneath this, this letter here.

MS. RANNEY: Sorry, not interrupt, but, your Honor, this is one of the exhibits for which plaintiffs have a competing translation. And I believe it's in defendant's binder it's PTX 1486.

THE COURT: 1486 is the other translation?

MS. RANNEY: Plaintiff's translation.

THE COURT: For 1060, is that it?

MS. RANNEY: Correct.

THE COURT: You can direct the witness if you'd like.

Sir, do you understand there's a translation at 1486? If you'd like to look in your binder.

THE WITNESS: A different translation?

THE COURT: And the other is 1060, correct? That's the defendant's translation.

MR. ALY: That's right. This wasn't, your Honor, one of the things they had raised. I think I could have probably used that if I knew.

THE WITNESS: PTX?

MS. RANNEY: Yes.

THE COURT: I'm sorry.

THE WITNESS: Okay.

Q. All right. Here we're looking at PTX 1486. We will use this. Here, you've got that one in front of you?

A. Yeah.

Q. And here what I wanted to make sure we were looking at together is there is a status report and it's talking about how the polymorphism screening at SSCI will most likely be completed by mid or late October.

Do you see that?

A. That's what it says.

Q. And at that point in time, this is again September 2001, there were tests that had been done and they found only two polymorphs A and B, correct? It says this resulted in the identification of at least two polymorphs?

A. The result there resulted in the identification of at least two polymorphs. That's what they say.

Q. When you see down below they've summarized the

temperature study that at temperatures below 40 degrees celsius or after the cessation of the mechanical stress, form B transforms back into form A.

Do you see that?

A. Yes.

Q. And it goes on the next sentence to say what you said, However, this does not happen sometimes until some time has elapsed, as little as six hours but possibly more than eight months.

Do you see that?

A. Correct.

Q. And there's actually one and only one theory that's provided for that at this time, the first theory that's provided that The cause of this partly kinetically very inhibited back transformation is not yet understood (it could depend on the impurities profile). Do you see that?

A. Exactly, not understood. And it could, it's speculation about what could happen. No further proof is provided anywhere.

Q. And it goes on at page, let's look at Page 12 of this PDF, still on PTX 1486, there's a slide here that's been presented and it has the title Two polymorphic modifications. And the two forms are identified there as form A and form B, right?

A. Yes. That's what it says. And again, it says this

behavior is not yet understood.

Q. And it says that underneath there the only reason given is that it might be due to impurities which inhibit the transformation from form B to form A, correct?

A. Right. This is one slide. This is part of an interim report in this kind of study where Grunenthal still didn't understand the polymorphic system, and neither did SSCI for that matter. This is pure speculation. It might be due to impurities. It was never further proved beyond that.

Q. This is the 2001 status at SSCI, right?

A. Yes, that's the date of the report.

Q. Let's look at the next status, DTX 1158. We're looking here at a research report?

A. Wait. This is now?

Q. DTX 1158.

A. Is now the translation of PTX?

Q. I am not aware of a translation issue with this one.

A. Okay. I don't know. So what number do I need?

MS. RANNEY: No translation issues here.

Q. DTX 1158.

A. I'm sorry, I don't have anything in my folder. That's empty. DTX?

Q. DTX.

A. DTX 1158 is empty in my folder.

Q. It looks like you got a special one. Let me make sure

we got the right one.

A. Wait, wait, let me look. No, it's not there. Hold on a second. Let me look back one. No.

Q. We've got an extra copy.

MR. ALY: May I approach?

THE COURT: Yes.

A. I don't have anything.

Q. All right. Dr. Bernstein, we've got DTX 1158 and we are looking at the cover page. It's a summary of polymorphism investigations now in 2003, right?

A. The date is 2003, June, yeah.

Q. One of the people on the prepared by list is Dr. Andreas Fischer? He is one of the co-inventors named on this '364?

A. Correct.

Q. Let's look at page 2 of this report. The second page of the document. We are going to look at this part right here, this table. There's a table on the bottom. And in 2003 the observation is made again that polymorph A is the one that's stable at room temperature, right?

A. Where? Okay. Yeah, right.

Q. And then on the right side of that stable polymorph B is the one identified as metastable at room temperature but stable at greater than 50 degrees celsius, right?

A. That's what the table says.

Q. And they discuss why this could be, at page 7. So, let's look at the text starting here, We determined, and you'll see that they put --

A. Wait, wait, let me go to page 7.

Q. Sure. It's the one ending in 571 as the production numbers.

A. Okay.

Q. And that one has in the top that We determined a cooling curve first to obtain the transition temperature form B to form A.

Do you see that?

A. I see it.

Q. So, that's basically they are saying normally we've seen other samples of B return to room temperature, return to form A at room temperature. So let's find out what that transition temperature is for the different samples that they were studying.

Do you agree with that?

A. Could I hear the question again?

Q. Sure. It was little long but I will basically -- do I understand the sentence correctly, we are reading it together here, that what they were trying to test to figure out when you take the B normally at room temperature converts to A. So they are trying to figure out what that transition temperature is where different samples of B convert or don't convert to A?

A. Well I don't agree with your introductory sentence that normally B converts to A, I don't agree, at room temperature. There are lots of instances where B doesn't convert to A. I will say there are instances where it does. But, I'm not sure I would use the term "normally".

Q. But SSCI had never seen a sample of form B that didn't convert to A at some point, right?

A. I don't know about all the SSCI experiments, but there are DSC, there are DSC traces that don't show the conversion from B to A once you get to room temperature. And I'm not sure they are in here, but I certainly have seen those.

Q. And then here?

A. And B exists. I mean B exists at room temperature. My testimony was full of examples of that.

Q. Let's look through the theories for what was discussed internally and at SSCI about why that could be, Dr. Bernstein. The describing of the protocol is On heating up we get the transition from A to B. And that's part of the process sometimes if you heat up A, you get B, right?

A. Right.

Q. And this method they are describing is useful to determine mixtures of form A and B and not just on the anyway low decreased heat of transition, but also on the B to A transition on cooling down.

Do you see that?

A. True. Yes, that's what it says.

Q. And the decreased heat of transition, just so we are on the same page, that is instead of transferring from B back to A at room temperature, it might be at a lower temperature that that transition occurs?

A. Or not at all.

Q. Or not at all. What they were then asking right underneath the box, Mr. Haw, we can go to the next section, we have made different attempts to try to explain this behavior for the decreased heat of transition. Do you see that?

A. Yes.

Q. And they have three different theories that they talk about. And we will scroll down to each of those.

And the first of the three theories is that they might have contamination with bromide in the sample. Do you see that?

A. I see what they say.

Q. Second is that there might be other impurities like by or degradation products, correct?

A. Yes.

Q. And the third is they might have polymorphic modification, that there's a third polymorph out there somewhere, right?

A. That's what it says.

Q. Now, they take a look at and discuss each of these

three theories. The first theory for crystallization of the corresponding bromide salt, they look at that. So this is, instead of forming Tapentadol hydrochloride, actually sometimes people might be forming Tapentadol hydrobromide, right?

A. Okay.

Q. Were you aware that this was an impurity theory that Grunenthal had discussed?

A. I think I've read it somewhere, yeah.

Q. And it goes on to say that this is an isotypic structure to the B modification of the chloride salt.

Do you see that?

A. I see that but I haven't seen any proof of that.

Q. Well, this is Grunenthal itself saying that in their experience it's isotypic, right?

A. Again, I've seen that in order for it to be isotypic, it would have to have the same x-ray powder diffraction pattern. And I haven't seen any evidence of that. That may be true, it may not be true. I can't confirm that for myself.

Q. First let me make sure we understand together what isotypic is. It means that it has the same XRD signal, correct?

A. It's not precisely the same because bromine is larger than chlorine and there will be some changes. But, if it's isotypic, one would expect a very similar pattern with some variations and the variations depend on going from one system

to another.

But, I haven't seen any isotypic x-ray powder diffraction pattern of the bromide instead of chloride. I just haven't seen it. And that's what they say, but I haven't any evidence.

And for me one of the things I always say to my students is theory guides but experiment decides. I haven't seen an experiment. I can't express an opinion on it until I can see it.

Q. Well, didn't they actually do the experiment? In the next sentence it says In the DSC data no thermal event could be found up to the melting point and down to minus 60 C.

And it's for that test reason that they conclude co-crystallization actually could be a reason for the decrease in the transition temperature?

A. No, they didn't prove anything. In order to prove the two systems are isotypic, you have to have the x-ray powder, you have to show that the bromide, you make the bromide and you measure the x-ray powder diffraction pattern and you put it next to the x-ray powder diffraction pattern like hydrochloride and you show that they are the same.

I haven't seen it. Maybe there are data out there. I haven't seen it. But, that's what has to be proved. And otherwise I can't say anything about this.

Q. Right. So, you don't have an opinion one way or the

other? You just know Grunenthal, when they were saying this, they hadn't shown it. Is that what you are saying?

A. I think we are in the process -- I think you have to understand something. We are in the process here of Grunenthal right from the beginning when they started realizing that they had more than one, they may have had more than one crystal form, it was a very common, it's a very common situation. They didn't know what was going on.

So, you can find a lot of information in the documentation over even a number of years, as was the case here, where there's speculation. It might be this. It might be that. We don't know. And this is very, very common.

Not only does it happen in the cases I have been involved in in industry as a consultant and also as an expert, but, it's happened in my own laboratory. We start with a system. We can't figure it out. It takes us awhile. So we speculate a lot. And this is what happened here. But, I have not seen proof that it's isotypic.

Q. And, in fact, Dr. Bernstein, for that theory the report goes on to say that The probability is not high, based on the samples SSCI had seen, because of the low amounts of the impurities that they found. Do you see that?

A. Right.

Q. But, you didn't look at the XRD to figure out what they would look like side by side, correct?

A. I am not aware there were any XRDs of these co-crystallization experiments or of the hydrobromide. I am not aware of them. Maybe there are, but, I haven't looked at them. No.

Q. So, nobody showed you the co-crystallization experiments that Grunenthal had, right?

A. No, I haven't seen it.

Q. All right. Let's look at the next page for this particular document on the second theory of impurities to Number 2. It goes down there.

The report goes on to say, There is a small number of impurities present in the batches that might affect the transition of the two polymorphic forms.

Do you see that, sir?

A. Yep. And the emphasis, my emphasis would be on the might, not proven.

Q. But, they go on to do systematic analysis of the different batches. This is by 2003, years after the table that you showed us on direct examination, and they give an analysis of that. Do you see that in Table 1?

A. Right. And as I've said before, if it's an impurity, if it is due to impurities, you have to show which impurities and what the level is. Otherwise, it's not proven to me.

Q. And on direct examination, so we're clear, you showed us a chart and said there's impurities at different amounts

with different samples. You didn't see a pattern between A and B, right?

A. That's correct.

Q. But, in this report they actually do actually what you said they should do, identify the impurities and show the level, didn't they?

A. But they had more data, which is what I discussed.

Q. Let's look at the data. It's right underneath that Table 1. If we can go back to the document. This paragraph here will show you the protocol that they had a special focus on two impurities, BN300 and BU351. Do you see that?

A. I see it.

Q. You testified on direct you weren't even sure what those were, correct?

A. I don't know the chemical identity of those two.

Q. Let's look at the next page, Page 9 of the report. And we are looking here at these two paragraphs, the first two paragraphs.

And the first paragraph here says let's look at BN300 and that seems to be without an influence up to 1.28 percent. Do you see that?

A. I see that.

Q. But then as soon as you go above that number, that 1.28 percent specific number with raising amount of this impurity, the transition temperature decreases.

In other words, there's more stable form B, right?

A. What is it this is based on? How many samples?

Q. Do you know how many samples were used here?

A. I can't, I don't see it here.

Q. And then they go on, do you agree with me the report that they provide is that after 1.28 percent, with rising amounts of that impurity, the transition temperature decreases? In other words, the room temperature stable B can stay more stable?

A. It slows down the transition. Okay. That's what it says.

Q. And they also will look at another impurity BU351. And here it says that it affects both the temperature decrease as well as the formation of a modification B that seems to be stable at room temperature.

Do you see that?

A. I see what it says, yeah.

Q. And it gives specific numbers for exactly where that occurs at more than .5 percent of BU351, that's where almost each sample they report had a cooling curve showing modification B, correct?

A. I'm not sure I understand the sentence here Almost each sample with a concentration of more than .5 percent BU351 reveals in the cooling curve of the DSC a rate of modification B. I don't know what that means, a rate of modification.

What is a rate of modification?

Q. Could it mean, sir, that you are starting to see some form B at room temperature that you wouldn't otherwise?

A. That's a phrase which the English means absolutely nothing to me.

Q. Let's be clear --

A. The DSC, a rate of modification B. Modification B is a structure. A rate is a velocity. A rate, so they are talking about the velocity of a structure. It doesn't say, maybe there's a word missing or what, but what's stated there doesn't make any sense. The English doesn't make any sense.

Q. Let's just, to round it out, look at the last sentence which I don't think we will have a disagreement about. It says At higher impurity levels, now we are looking at greater than 1.8 percent in Table 1, the only product is form B and in between mixtures of A and B are formed.

Do you see that?

A. That's what it says.

Q. So, the report that they found is that if you go above 1.8 percent of BU351, they only saw form B, correct?

A. Okay.

Q. Now, let's look at Page 10. I said there were three theories they considered and Page 10 has a third theory, this part here. And it says in Step 3, this was whether they really had maybe found a third polymorph. Do you remember that one?

A. That was a possibility but it was never, I haven't seen any evidence of a third form.

Q. And in fact they ruled it out after some extensive investigations, correct?

A. Okay.

Q. And the conclusion that they reached in 2003 is that the existence of an intermediate polymorphic form is most unlikely, concerning the current results. Do you see that?

A. I see that's the conclusion, yes.

Q. And, by the way, while we're at this document, I want to make sure that the differences between form A and B, they are, biologically they don't make any difference, right?

A. I understand the physiological absorption is the same.

Q. And the solubility curves, they are what you call identical here, right?

A. I don't recall. But, I don't recall this, the solubility curve. But, I wouldn't be surprised. I think they are quite similar.

Q. Let's look at them together on Page 15 of this document of Exhibit 1158. And here we have the curves in figure 7. These are the dissolution testing that they did and showed the solubility over time.

Do you see that of polymorphs A and B?

A. That's a dissolution curve, yes.

Q. And the text under that analyses is right it says the

curves are identical, variation between the 5 and 10 minutes values can lead back to the dissolution of the gelatine capsules.

Do you see that?

A. That's what it says.

Q. As far as you are aware, because the solubility is the same, that's what pharmacists or physicians or drug developers look at to determine whether or not there would be any importance to study from an FDA point of view.

Is that right?

A. That's one of the factors.

Q. And now let's look at PTX 507. Well, sorry, PTX 379. Let's look at that.

Now, we have the Crystallics report. That's their final report in May 2003.

Do you see that?

A. I see it.

Q. And if we look at Page 10. In Page 10 they've got to Step 3 Effect of Impurities.

Do you see that section?

A. I see it.

Q. This section has been discussed in other testimony but I want to look at the data with you. And that's at Page 23 referring to this Step 3. And you see this table here is the Step 3 table.

Do you see that?

A. That's what it says.

Q. And in terms of the experience that Crystallics had, they also found that only with impurities can you get form B, right?

A. I don't see that conclusion.

Q. All right. Let's look through the data. There's some factors here that are called seeding. We looked at seeding and we talked about that earlier, correct?

A. You're talking about factor C, the cut right? The seed amount?

Q. The seed amount. Putting aside seed amount, because seeding is a separate issue for this case but for this case we have impurity A which is factor A. And we've got another impurity which is called factor B. And what they've done here is they said let's add, on purpose, certain percentages of those impurities. Do you see that?

A. Could you go through that again, please?

Q. Sure. What they've done in the study is they have put, on purpose, certain percentages of these two impurities identified as factors A and factors B, correct?

A. Yes.

Q. You don't know what those impurities are, right?

A. I have no idea.

Q. And when they added in any percentage of either factor

A or factor B but didn't seed it with something, that resulted in some form B, correct?

A. What you're directing me to is the result in response in five.

Is that right.

Q. Response five. That's where they got that polymorph?

A. So, what you're saying is standard two has factor A and resulted in a mixture of A and B. And standard three has factor B and that results in a mixture of A and B and standard four has both factor A and factor B and results in a mixture of A and B.

And then standard 9 has just factor B and that results in a mixture of A and B. Is that what you -- is that the question you're asking?

Q. Yes, sir.

A. Okay. That's what the table says.

Q. All right. Now, in terms of impurities, I know you testified why but I just want to make clear that you agree if we had the Marita Mueller sample to test today, we could test it to see what impurities are there of the type that are being referenced here?

A. You could, but it doesn't make any difference because she did a faithful reproduction of it. And I show you the evidence she got form B. She got the x-ray powder diffraction pattern of form B. The fingerprint, it's form B. It doesn't

matter. It doesn't really matter why she got form B, she got form B.

Q. Well, Dr. Bernstein, if Marita Mueller agreed, if she herself agreed she didn't follow example 25, then it wouldn't be pertinent to the analysis of whether example 25 anticipated even if she got form B, right?

A. Well, to the best of my knowledge and according to Dr. Roush's testimony, she did follow example 25. So, I don't think, for me, that's not an issue.

Q. That's what I want to make sure. This is not your opinion. You are relying on Dr. Roush for that?

A. Absolutely.

Q. Similarly for the batch 0 that existed at some point, we can't, that doesn't exist anymore so we can't test it to find out what impurities it had and how it might have been made incorrectly?

A. That's correct.

Q. I do want to take a look at the examples in the '364 patent. But, we don't need to put it up right now.

I just want to make sure when you were saying that the patent said it started with example 25 from the other patents, were you saying that it was form A, sir?

A. No, I didn't. I didn't say it started with example 25. Put it up and we will see what it says.

Q. All right. Let's look at DTX 304. That's the '364

patent. And we want to look at example two.

A. So, it was prepared according to example 25. And I explained that at the time this was written that if somebody was reading this patent and wanted to go out and buy that material, they couldn't find it.

So, the only, so the inventor had to explain, to teach a person of skill in the art where can you get this stuff. So you go back to example 25 and you make it.

Q. And what I want to make sure that you and I agree on right now is do you agree or not that when it's referring in the patent to some starting material that was made according to example 25 actually was form A?

A. I wouldn't say that. From the best of my knowledge it was no, example 25 gives you form B. Why would it be form A?

Q. Have you gone back, sir, to look at the tests, where this came from, this example came from, and whether or not that first sentence where it said it was example 25 was form A Tapentadol or form B Tapentadol?

A. I haven't gone back because it doesn't make any difference. What this is is a crystallization. It doesn't matter, really doesn't matter whether it's form A or it's form B. You are doing a recrystallization. So, you are going to dissolve the material. Once it dissolves, it doesn't matter which form it was to begin with.

Q. Let me ask that question so I can have that as a

response answer.

Does it matter what you start with as a solid if you are doing it in solution and getting a recrystallization?

A. It doesn't matter which form you start with.

Q. So, now if we're looking at, in this example, to go back to the question I asked you, do you know whether or not that starting material that they said was according to example 25, was form A or not?

A. Now you're talking about the notebook record of what went into this example.

Q. Notebook record or any other record, sir.

A. I don't know. But, it wouldn't make any difference to me because whatever -- I assume it's form B because it was made according to example 25 and it was dissolved. If it happened to be form A, it wouldn't make any difference about the nature of this example.

Q. I hear you saying that it wouldn't make any difference. But, do you know whether or not the Patent Office would have been interested to know whether the invention here was taking form B and making it into form A or starting with form A and making it into form A?

MS. RANNEY: Objection, your Honor. Dr. Bernstein doesn't really have, doesn't have any knowledge of what the Patent Office would have said.

THE COURT: Sustained.

Q. Dr. Bernstein, you're saying that they had -- you are saying that it doesn't matter. But, do you know what it was that Grunenthal told the Patent Office about this particular form?

A. In this example 2, did Grunenthal tell the Patent Office which form of the compound they used in performing this?

Q. That's my question.

A. I am not aware of that information.

Q. And did Grunenthal say anywhere in the patent what form you get when you make the recipe according to example 25?

A. Could I hear that question again?

Q. Sure. Did Grunenthal tell the Patent Office anywhere in the patent what form one should get when they follow example 25 from the prior art?

A. I don't recall what Grunenthal told the Patent Office. I haven't seen a file wrapper. I don't know. But, as a chemist, to be honest with you, it doesn't make any difference in this example.

Q. Well, let's look at the top of column 3 of the '364 patent. So, we are still at DTX 304, the first full paragraph. It says, they write Grunenthal in the patent, The process starts from crystalline form B prepared according to U.S. patent number '737 patent or the '558 patent or the European '475 patent, it's all the same specification.

Do you see that?

A. I see it.

Q. And then they are talking about how they are going to take that starting material, which is form B as they report in this part of the patent, and say they are going to turn it into form A with the different examples that they discussed, correct?

A. That's what it says.

Q. And so when they really did the experiment, did you know, Dr. Bernstein, that example 2 and other examples actually started with form A, even though they put in the patent that it was made according to example 25?

A. I didn't. But frankly, I have no reason to doubt it because example 25 makes form B.

Q. Well, let me ask you this, if we look at the particular report, DTX 141, 144 is the interrogatory responses, and we will look at Page 9. And this is the interrogatory responses from Grunenthal, plaintiffs in this case. And when you look at the box here and you see that for examples 2 and 3 the reference is to a document with the production number starting in 21090. Do you see that?

A. No, oh, okay.

Q. It's the same document then that's for example 3, right?

A. Okay.

Q. It's also for example 5, that same Document 21090?

A. Okay.
Q. Nine, example nine, the same Document 21090?
A. I see it.
Q. And example 11, that's the same Document 21090?
A. Okay.
Q. Let's look at that document with the 21090 that's going to be --
A. To be perfectly honest with you I don't know what you're showing me here. I have no idea what this is.
Q. You haven't seen the interrogatory responses?
A. No.
Q. Let's go back a page then I will show you what we're looking at. Go back one more.
This is the response that plaintiffs gave when the interrogatory was put to them in interrogatory Number 21 to explain the basis for the examples that were in the '364 patent, the one that you've provided opinions on.
A. Okay. I don't think I recall ever having seen this before.
Q. They didn't show you where the examples came from?
A. No, I haven't seen this document.
Q. Oh, you haven't seen it?
A. The interrogatories I haven't seen.
Q. Okay. Do you disagree with the response in the interrogatories?

A. Do I disagree about what?

Q. About where the materials came from. In other words, do you have other information that's not here about where the examples in the patent could have come from?

A. I don't have any reason to agree with you or disagree with you. I mean I'm just not familiar with this document or with the interrogatories. And I don't know where the examples, except for what's written in the patent that you just showed me, I don't know where the samples came from.

I said I haven't seen a file wrapper so I don't know. I'm not familiar with those details.

Q. Let's look at those details. DTX 1001, the document we looked at, the 2006 polymorph screen. This is DTX polymorph screen with enclosures is the report from SSCI. You can look at the bottom half of this. It just says it's an enclosure of a report from SSCI. Do you see that? Do you see that?

A. Yes.

Q. And then on Page 3 of the document -- and by the way, sorry, if we can go back to Page 1. The production number on Page 1 is 21090. Do you see that?

A. I see that.

Q. And then if we go to Page 3, you will see that the attachment is this polymorph screen from SSCI, right?

A. I see that.

Q. Now, if we go to Page 5, you will see that the starting material, the samples here is the CG 5503 sample received from Grunenthal as summarized in Table 1.

Do you see that?

A. I see that.

Q. And now if you go forward to Table 1 which is on Page 13 of the document, the very top table, it says that the sample received from Grunenthal was XRD result of form A. Do you see that?

A. That's what it says.

Q. When we are looking at the '364 patent and if we take them at their word, what Grunenthal was telling the Patent Office for example 2 when they said it was material according to example 25 of the prior art, that was this form A material that was used in those experiments, correct?

A. You're going to have to go through the identification for me again. This says, this says this was lot CEHS98-99 and CG5503. That's the SSCI internal number.

Q. That's right.

A. Okay. And then CEHS98-99 is what?

Q. The material they labeled when they received it. Did you know that?

A. I thought I just said no but then there's an SSCI number. You're going to have to track it for me. I don't --

Q. Let me just --

A. I lost track of where the sample is. I mean I can't confirm anything because I've gotten lost to where this sample started out and where we got to.

Q. We can retrace the steps but let me ask you, Table 1, in the interest of time, you see there is only one sample lot that SSCI received from Grunenthal, correct?

A. This table shows one entry. What else they received, I don't know. I mean I notice this report has 180 some odd pages and I'm not familiar with the whole report. So, you've shown me one table with one entry and that's what it says. It says what it says. I can't argue with that.

Q. This is the same report that was referenced in those interrogatory responses we looked at, right?

A. I don't remember the number. I'm not familiar with the number in the interrogatory report. But, I will assume that that's correct.

MR. ALY: Your Honor, I was handed a note about the timing so I must be sensitive to the time. I do still have about 20 minutes of material on the obviousness opinions that the expert offered.

So, maybe I could address those now if you'd like. But, in the morning would also be fine. It's like a breaking point is what I'm saying.

THE COURT: It's already, it's like it's almost 6:20 at this point. Counsel, I'm thinking we should probably

break.

MS. RANNEY: I think it's time to break.

THE COURT: I think so too actually. All right. So, let us conclude for the evening.

Sir, you will remain under oath. But, we will pick up your testimony tomorrow morning.

Let's decide on a time then. With that also do not speak to your Counsel regarding your testimony.

Shall we do 9 o'clock tomorrow morning as well?

MR. ALY: That's fine with me, your Honor.

THE COURT: Is that good?

MR. CONNOLLY: That's fine with us, your Honor.

MS. RANNEY: And plaintiffs.

THE COURT: So, we will start 9 o'clock tomorrow morning. Any other issues before we disband for the evening? Anything? No.

MR. ALY: That's a brave question, your Honor.

THE COURT: That concludes our testimony for the evening. We will see you tomorrow morning at 9 o'clock. Thank you so much. Thank you, everyone. Take care.

ATTORNEYS: Thank you, your Honor.

(Whereupon the matter was concluded)